# STIC Search Report
## Biotech-Chem Library

**STIC Database Tracking Number: 124744**

**TO: David Lukton**
**Location: REM-3B75/3C70**
**Art Unit: 1653**
**June 18, 2004**

**Case Serial Number: 10037358**

**From: P. Sheppard**
**Location: Remsen Building**
**Phone: (571) 272-2529**

**sheppard@uspto.gov**

## Search Notes

SEARCH REQUEST FORM
(STIC)

Access DB# _____

Requestor's Name: David Lukton Examiner number: 71263 Date:

Art Unit: 1653 Phone number: 571-272-0952 Serial Number: 10/037358

Mail Box: 3-C-70 Examiner Rm: 3-B-75 Results format: paper

* * * *

Title: DMT-TIC DI-AND TRI-PEPTIDIC DERIVATIVES AND RELATED COMPOSITIONS AND METHODS OF USE

Applicants: LAZARUS, LAWRENCE H.; SALVADORI, SEVERO

Earliest Priority Date: 3/24/00

* * * *

Applicants are claiming the following compounds, wherein R' is any of the substituents listed on the attached sheet

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=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 16:40:35 ON 18 JUN 2004
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FILE COVERS 1907 - 18 Jun 2004  VOL 140 ISS 26
FILE LAST UPDATED: 17 Jun 2004  (20040617/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


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L1                STR
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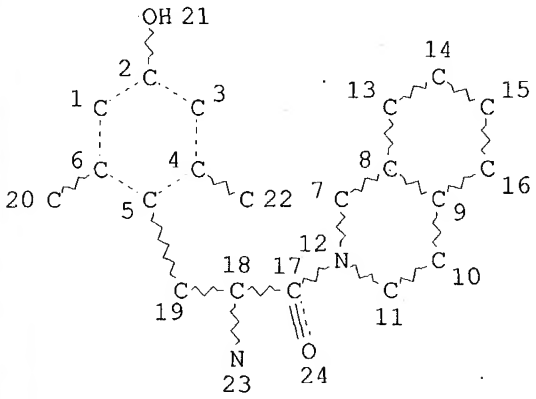


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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS  24

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L6               STR
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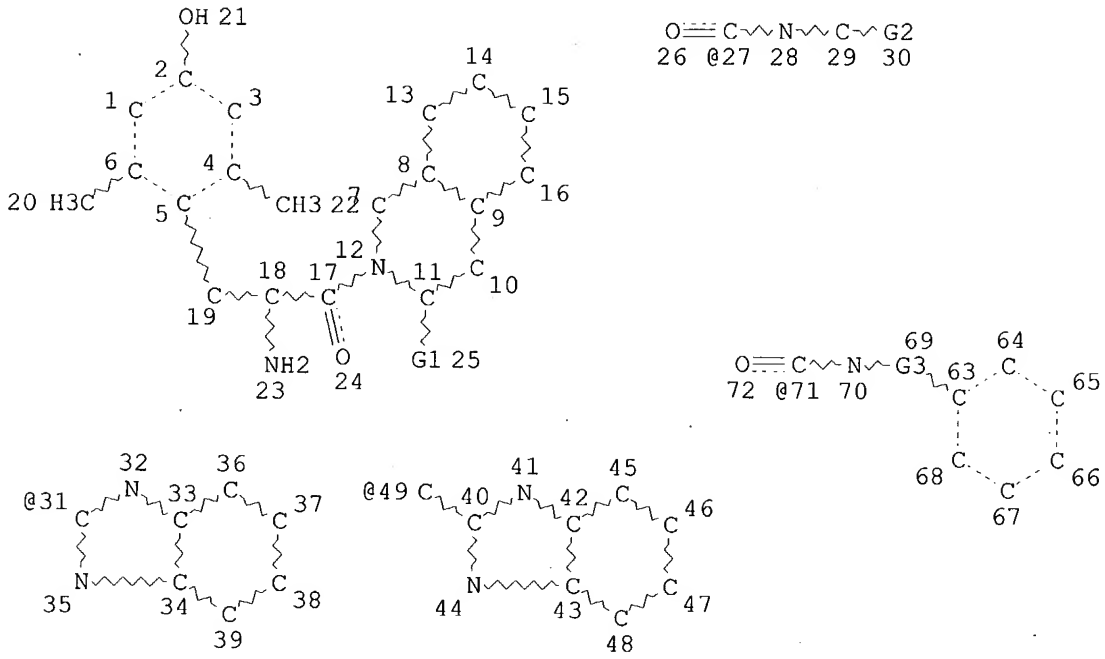
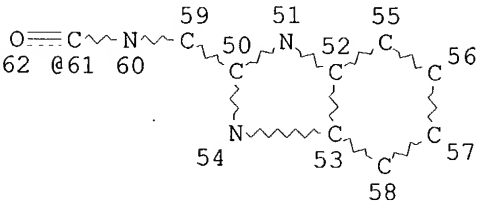




Page 1-A



Page 2-A
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 72

STEREO ATTRIBUTES: NONE
L7 34 SEA FILE=REGISTRY SUB=L5 SSS FUL L6
L8 7 SEA FILE=HCAPLUS ABB=ON PLU=ON L7

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L8 ANSWER 1 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:923401 HCAPLUS
DOCUMENT NUMBER: 140:263738
TITLE: Synthesis and opioid activity of N,N-Dimethyl-Dmt-Tic-NH-CH(R)-R' analogues: acquisition of potent δ

antagonism
AUTHOR(S): Balboni, Gianfranco; Salvadori, Severo; Guerrini, Remo; Negri, Lucia; Giannini, Elisa; Bryant, Sharon D.; Jinsmaa, Yunden; Lazarus, Lawrence H.
CORPORATE SOURCE: Department of Toxicology, University of Cagliary, Cagliary, I-09126, Italy
SOURCE: Bioorganic & Medicinal Chemistry (2003), 11(24), 5435-5441
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB N,N-Dimethylation of the H-Dmt-Tic-NH-CH(R)-R' series of compds. produced no significant effect on the high δ-opioid receptor affinity (Ki=0.035-0.454 nM), but dramatically decreased that for the μ-opioid receptor. The effect of N-methylation was independent of the length of the linker (R); however, the bioactivities were affected by the chemical composition of the third aromatic group (R'): Ph (Ph) (5'-8') elicited a greater reduction in μ-affinity (40-70-fold) compared to analogs containing 1H-benzimidazole-2-yl (Bid) (9-fold). The major consequences of N,N-dimethylation on in vitro bioactivity were: (i) a loss of δ-agonism coupled with the appearance of potent δ antagonism; and (ii) a consistent loss of μ-affinity resulted in enhanced δ-opioid receptor selectivity. With the exception of one compound, the change in the hydrophobic environment at the N-terminus and formation of a tertiary amine by N,N-dimethylation in analogs of the Dmt-Tic pharmacophore produced potent δ-selective antagonists.
IT **403652-09-5P 403652-10-8P 403652-11-9P**
**403652-12-0P 403652-13-1P 403652-14-2P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and opioid activity of Dmt-Tic analogs)
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:892613 HCAPLUS
DOCUMENT NUMBER: 139:381482
TITLE: Preparation of 4-phenylimidazoles and related compounds as opioid receptor modulators for the treatment of pain and gastrointestinal disorders
INVENTOR(S): Breslin, Henry J.; He, Wei; Kavash, Robert W.
PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.
SOURCE: PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003092688 | A2 | 20031113 | WO 2003-US11872 | 20030417 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,

NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004010014 A1 20040115 US 2003-400006 20030326
PRIORITY APPLN. INFO.: US 2002-376406P P 20020429
US 2003-400006 A 20030326
OTHER SOURCE(S): MARPAT 139:381482
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [X = O, S, N(R14), etc.; R14 = H, alkyl, aryl, etc.; R1 = (un)substituted benzimidazole, benzoxazole, benzothiazole, etc.; R2 = (un)substituted CH2CH2, e.g., halo, phenylmethyl; R3, R4 = H, alkyl aryl, etc.; R5, R6 = H, alkyl, aryl, etc.; n, r = 0-2; L = O, S, H2, etc.; R8, R9 = H or alkyl with provisos; s = 0-3; R9 = H, alkyl; R10, R11 = H, alkyl; p = 0-3; R12, R13 = H, alkyl, formyl, etc.; Ar = Ph, naphthyl, heteroaryl; Z = 0-4 substituents consisting of halo, alkyl, alkoxy, etc.] and their pharmaceutically acceptable salts were prepared For example, reductive amination of acetone with amine II, e.g., prepared from (3S)-3,4-dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-tert-Bu ester in 4-steps, followed by phenol deprotection afforded claimed phenylimidazole III. In rat brain δ-opioid receptor binding assays, approx. 90-examples of compds. I exhibited Ki values ranging from 0.06-50,000 nM, e.g., the Ki value of phenylimidazole III was 11.9 nM. Compds. I are claimed useful as opioid receptor modulators, antagonists and agonists for the treatment of pain and gastrointestinal disorders.

IT **623949-66-6P 623949-67-7P 623949-68-8P**
**623949-83-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(target compound; preparation of 4-phenylimidazoles and related compds. as opioid receptor modulators for the treatment of pain and gastrointestinal disorders)

L8 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:851286 HCAPLUS
DOCUMENT NUMBER: 138:66167
TITLE: Potent δ-Opioid Receptor Agonists Containing the Dmt-Tic Pharmacophore
AUTHOR(S): Balboni, Gianfranco; Salvadori, Severo; Guerrini, Remo; Negri, Lucia; Giannini, Elisa; Jinsmaa, Yunden; Bryant, Sharon D.; Lazarus, Lawrence H.
CORPORATE SOURCE: Department of Toxicology, University of Cagliari, Cagliari, I-09126, Italy
SOURCE: Journal of Medicinal Chemistry (2002), 45(25), 5556-5563
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 138:66167

AB Conversion of δ-opioid receptor antagonists containing the 2',6'-dimethyl-L-tyrosine (Dmt)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) pharmacophore into potent δ-agonists required a third heteroarom. nucleus, such as 1H-benzimidazole-2-yl (Bid) and a linker of specified length both located C-terminally to Tic in the general formula H-Dmt-Tic-NH-CH(R)-R'. The distance between Tic and Bid is a determining factor responsible for the acquisition of δ agonism or δ antagonism. Compds. containing a C-terminal Ala, Asp, or Asn with an amide or

free acid group served as δ-antagonist controls lacking the third heteroarom. ring. A change in chirality of the spacer or inclusion of a neg. charge via derivs. of Asp resulted in potent δ agonism and moderate μ agonism, although δ-receptor affinity decreased about 10-fold for one peptide while μ affinity fell by over 2 orders of magnitude. Repositioning of the neg. charge in the linker altered activity:H-Dmt-Tic-NH-CH(CH2-Bid)COOH maintained high δ affinity (Ki = 0.042 nM) and δ agonism (IC50 = 0.015 nM), but attachment of the free acid group to Bid [H-Dmt-Tic-NH-CH2-Bid(CH2-COOH)] reconstituted δ antagonism (Ke = 0.27 nM). The data demonstrate that a linker separating the Dmt-Tic pharmacophore and Bid, regardless of the presence of a neg. charge, is important in the acquisition of opioids exhibiting potent δ agonism and weak μ agonism from a parent δ antagonist.

IT **403652-10-8 403652-11-9 480446-47-7**
RL: PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
(preparation and structure-activity relationship of potent δ-opioid receptor agonists containing the Dmt-Tic pharmacophore)

IT **480446-43-3P 480446-44-4P 480446-45-5P 480446-46-6P**
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and structure-activity relationship of potent δ-opioid receptor agonists containing the Dmt-Tic pharmacophore)

IT **480446-49-9P 480446-50-2P 480446-51-3P 480446-54-6P 480446-57-9P**
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(preparation and structure-activity relationship of potent δ-opioid receptor agonists containing the Dmt-Tic pharmacophore)

IT **480446-89-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and structure-activity relationship of potent δ-opioid receptor agonists containing the Dmt-Tic pharmacophore)

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:833557 HCAPLUS
DOCUMENT NUMBER: 137:338140
TITLE: Preparation of 2',6'-dimethyltyrosinyl-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (Dmt-tic) di- and tri-peptidic derivatives as δ-opioid antagonists
INVENTOR(S): Lazarus, Lawrence H.; Salvadori, Severo
PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA
SOURCE: U.S. Pat. Appl. Publ., 27 pp., Cont.-in-part of U. S. Ser. No. 814,558.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2002161189 | A1 | 20021031 | US 2001-37358 | 20011221 |
| WO 2003062261 | A2 | 20030731 | WO 2002-US40770 | 20021220 |
| WO 2003062261 | A3 | 20040212 | | |

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PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-192128P P 20000324
US 2001-814558 A2 20010322
US 2001-37358 A 20011221

OTHER SOURCE(S): MARPAT 137:338140

AB The invention relates to di- and tripeptidic derivs. comprising the pharmacophore H-Dmt-Tic-X-Y (Tic = 2',6'-dimethyltyrosine, Tic = 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, X is a spacer comprising one or more amino acid residues and Y comprises an aromatic group) and related compns. and methods of use. The Dmt-Tic pharmacophore represents a distinct class of δ-opioid antagonists. Thus, H-Dmt-Tic-NH-tetrazol-5-yl.TFA was prepared by coupling of Boc-protected Dmt with H-Tic-OMe, amidation with 5-aminotetrazole and deprotection. Results of binding of compds. of the invention to α-opioid and μ-opioid receptors are tabulated. The binding data are discussed in terms of variation in structure of the compds.

IT **474013-80-4P 474013-82-6P 474013-84-8P**
**474013-86-0P 474013-89-3P 474015-40-2P**
**474015-45-7P 474015-50-4P 474015-53-7P**
**474015-57-1P 474015-63-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of dimethyltyrosinyltetrahydroisoquinolinecarboxylic acid (Dmt-tic) di- and tri-peptidic derivs. as δ-opioid antagonists)

L8 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:692538 HCAPLUS
DOCUMENT NUMBER: 138:338458
TITLE: Synthesis and pharmacological activity of Dmt-Tic analogs with highly potent agonist and antagonist/agonist opioid activity
AUTHOR(S): Guerrini, Remo; Balboni, Gianfranco; Rizzi, Daniela; Calo, Girolamo; Bryant, Sharon D.; Lazarus, Lawrence H.; Salvadori, Severo
CORPORATE SOURCE: Department of Pharmaceutical Sciences, University of Ferrara, Ferrara, 44-100, Italy
SOURCE: Peptides: The Wave of the Future, Proceedings of the Second International and the Seventeenth American Peptide Symposium, San Diego, CA, United States, June 9-14, 2001 (2001), 679-680. Editor(s): Lebl, Michal; Houghten, Richard A. American Peptide Society: San Diego, Calif.
CODEN: 69DBAL; ISBN: 0-9715560-0-8
DOCUMENT TYPE: Conference
LANGUAGE: English

AB A symposium report. Dmt-Tic analogs (Dmt = 2,6-dimethyl-L-tyrosine residue, Tic = L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid residue) were synthesized and their in vitro opioid activities determined Introduction of a pharmacophore [N-1H-benzimidazol-2-yl (Bid), N-Ph, or N-benzyl amide] at the C-terminal of Dmt-Tic significantly increased μ receptor affinity and induced agonist activity in the guinea pig ileum. In the mouse vas deferens assay, the compds. were agonists only when the second pharmacophore (Bid or N-Ph amide) was located at a minimal distance from the aromatic nuclei Dmt-Tic. Bid was better than N-Ph amide for activation of the δ-opioid receptor.

IT **403652-10-8P 403652-11-9P 403652-12-0P**

**403652-13-1P 403652-14-2P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and pharmacol. activity of Dmt-Tic analogs with highly potent agonist and antagonist/agonist opioid activity)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:14209 HCAPLUS
DOCUMENT NUMBER: 136:226323
TITLE: Evaluation of the Dmt-Tic Pharmacophore: Conversion of a Potent δ-Opioid Receptor Antagonist into a Potent δ Agonist and Ligands with Mixed Properties
AUTHOR(S): Balboni, Gianfranco; Guerrini, Remo; Salvadori, Severo; Bianchi, Clementina; Rizzi, Daniela; Bryant, Sharon D.; Lazarus, Lawrence H.
CORPORATE SOURCE: Department of Toxicology, University of Cagliari, Cagliari, 09126, Italy
SOURCE: Journal of Medicinal Chemistry (2002), 45(3), 713-720
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Analogs of the 2',6'-dimethyl-L-tyrosine (Dmt)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) pharmacophore were prepared to test the hypothesis that a "spacer" and a third aromatic center in opioid peptides are required to convert a δ-antagonist into ligands with δ-agonist or with mixed δ-antagonist/μ-agonist properties. Potent δ-agonists and bifunctional compds. with high δ- and μ-opioid receptor affinities were obtained by varying the spacer length [none, NH-CH2, NH-CH2-CH2, Gly-NH-CH2] and C-terminal aromatic nucleus [1H-benzimidazole-2-yl, Ph and benzyl groups]. C-terminal modification primarily affected μ-opioid receptor affinities, which increased maximally 1700-fold relative to the prototype δ-antagonist H-Dmt-Tic-NH2 and differentially modified bioactivity. In the absence of a spacer (1), the analog exhibited dual δ-agonism (pEC50, 7.28) and δ-antagonism (pA2, 7.90). H-Dmt-Tic-NH-CH2-1H-benzimidazol-2-yl (Bid) (2) became a highly potent δ-agonist (pEC50, 9.90), slightly greater than deltorphin C (pEC50, 9.56), with μ-agonism (pE50, 7.57), while H-Dmt-Tic-Gly-NH-CH2-Bid (4) retained potent δ-antagonism (pA2, 9.0) but with an order of magnitude less μ-agonism. Similarly, H-Dmt-Tic-Gly-NH-Ph (5) had nearly equivalent high δ-agonism (pEC50, 8.52) and μ-agonism (pEC50, 8.59), while H-Dmt-Tic-Gly-NH-CH2-Ph (6) whose spacer was longer by a single methylene group exhibited potent δ-antagonism (pA2, 9.25) and very high μ-agonism (pEC50, 8.57). These data confirm that the distance between the Dmt-Tic pharmacophore and a third aromatic nucleus is an important criterion in converting Dmt-Tic from a highly potent δ-antagonist into a potent δ-agonist or into ligands with mixed δ- and μ-opioid properties.
IT **403652-09-5P 403652-10-8P 403652-11-9P**
**403652-12-0P 403652-13-1P 403652-14-2P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(evaluation of Dmt-Tic pharmacophore: conversion of a potent δ-opioid receptor antagonist into a potent δ agonist and ligands with mixed properties)
REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:828316 HCAPLUS

DOCUMENT NUMBER: 134:66089
TITLE: Opioid pseudopeptides containing heteroaromatic or heteroaliphatic nuclei
AUTHOR(S): Balboni, G.; Salvadori, S.; Guerrini, R.; Bianchi, C.; Santagada, V.; Calliendo, G.; Bryant, S. D.; Lazarus, L. H.
CORPORATE SOURCE: Department of Toxicology, University of Cagliari, Cagliari, I-09126, Italy
SOURCE: Peptides (New York) (2000), 21(11), 1663-1671
CODEN: PPTDD5; ISSN: 0196-9781
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In lieu of H-Dmt-Tic-OH, H-Dmt-analogs included 2-amino-3(1H-benzoimidazol-2-yl)-propionic acid, N(Bzl)Gly, L-octahydroindole-2-carboxylic acid, [3S-(3α,4aβ,8aβ)]-decahydro-3-isoquinoline carboxylic acid, benzimidazole-, pyridoindole- or spiroinden-derivs., or C-terminally modified. L- Or D-Ala, Sar, or Pro were spacers between aromatic nuclei. Only H-Dmt-(Xaa-)-pyridoindole exhibited high affinities with δ and μ antagonism. The peptides competed equally against [3H]DPDPE (δ agonist) or [3H]N,N(CH3)2-Dmt-Tic-OH (δ antagonist) signaling a single δ binding site. The data confirm the importance of Tic for δ affinity and antagonism, while heterocyclic or heteroaliph. nuclei, or spacer exert effects on μ- and δ-receptor properties.

IT **314756-49-5P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(opioid pseudopeptides containing heteroarom. or heteroaliph. nuclei)

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FILE LAST UPDATED: 01 May 1997 (19970501/UP)

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L9 0 L7

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STRUCTURE FILE UPDATES: 17 JUN 2004 HIGHEST RN 694921-36-3
DICTIONARY FILE UPDATES: 17 JUN 2004 HIGHEST RN 694921-36-3

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

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Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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L7 ANSWER 1 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 623949-83-7 REGISTRY
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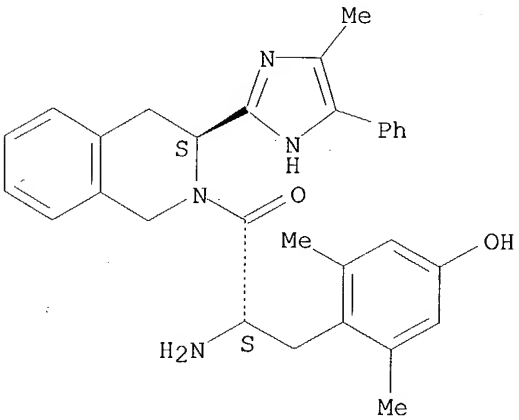
FS STEREOSEARCH
MF C30 H32 N4 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.



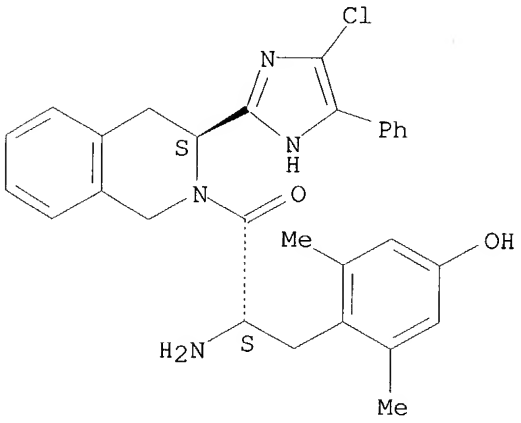
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:381482

L7 ANSWER 2 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 623949-68-8 REGISTRY
CN Isoquinoline, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-3-(4-chloro-5-phenyl-1H-imidazol-2-yl)-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C29 H29 Cl N4 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.



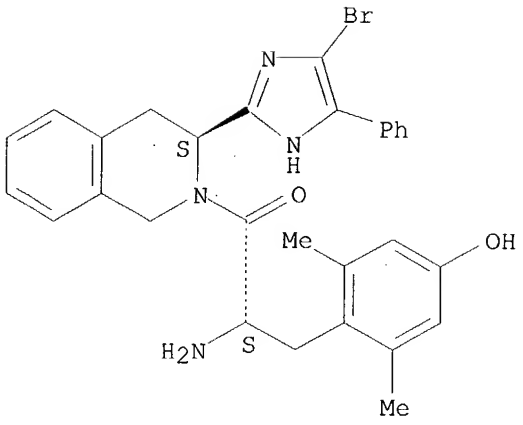

**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:381482

L7 ANSWER 3 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 623949-67-7 REGISTRY
CN Isoquinoline, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-3-(4-bromo-5-phenyl-1H-imidazol-2-yl)-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C29 H29 Br N4 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.



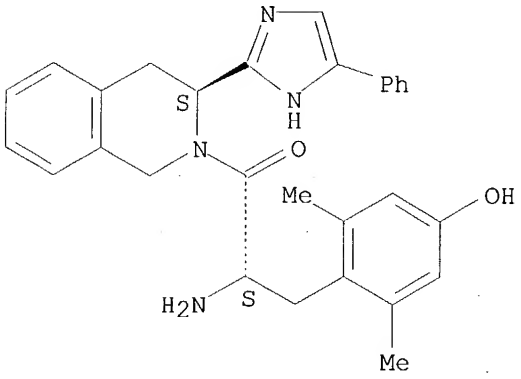

**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:381482

L7 ANSWER 4 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 623949-66-6 REGISTRY
CN Isoquinoline, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-3-(4-phenyl-1H-imidazol-2-yl)-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C29 H30 N4 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

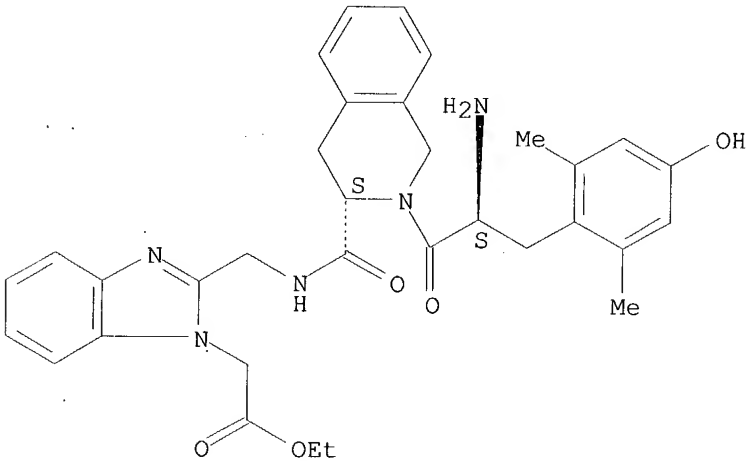
REFERENCE 1: 139:381482

L7 ANSWER 5 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 480446-89-7 REGISTRY
CN 1H-Benzimidazole-1-acetic acid, 2-[[[[(3S)-2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinyl]carbonyl]amino]methyl]-, ethyl ester, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C33 H37 N5 O5 .. 2 C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, CASREACT
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: PREP (Preparation); RACT (Reactant or reagent)

CM 1

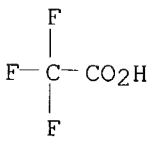
CRN 480446-88-6
CMF C33 H37 N5 O5

Absolute stereochemistry. Rotation (-).




CM 2

CRN 76-05-1
CMF C2 H F3 O2



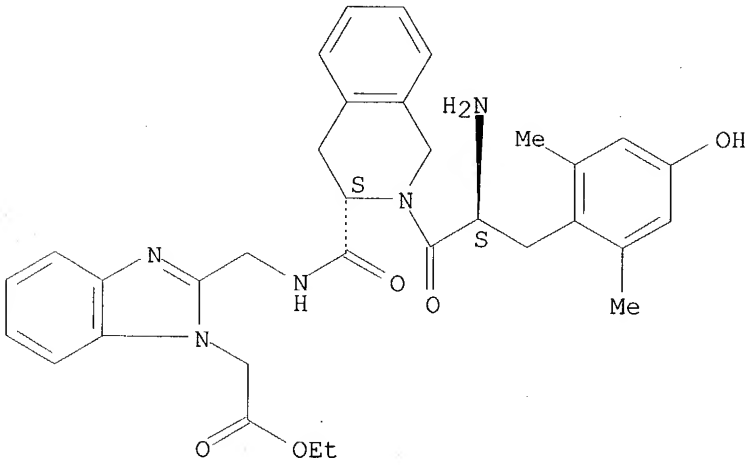

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 138:66167

L7 ANSWER 6 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 480446-88-6 REGISTRY
CN 1H-Benzimidazole-1-acetic acid, 2-[[[[(3S)-2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-3-

isoquinolinyl]carbonyl]amino]methyl]-, ethyl ester (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C33 H37 N5 O5
CI COM
SR CA

Absolute stereochemistry. Rotation (-).



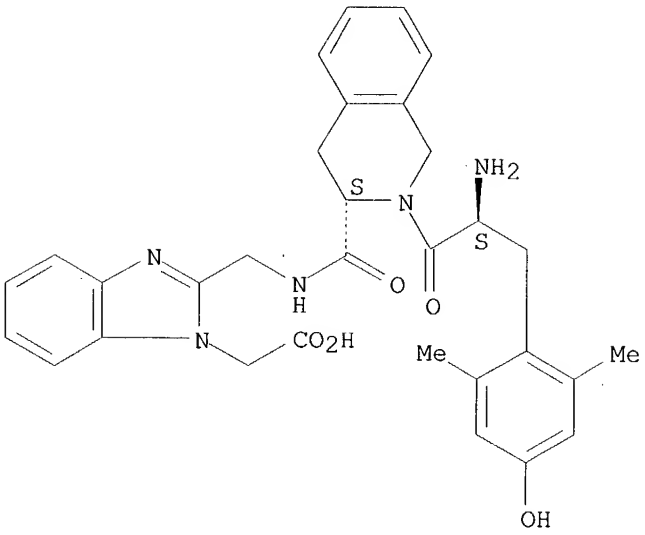

**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

L7 ANSWER 7 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 480446-57-9 REGISTRY
CN 1H-Benzimidazole-1-acetic acid, 2-[[[[(3S)-2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinyl]carbonyl]amino]methyl]-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H33 N5 O5 . 2 C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: PREP (Preparation); PRP (Properties)

CM 1

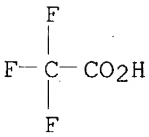
CRN 480446-46-6
CMF C31 H33 N5 O5

Absolute stereochemistry. Rotation (-).



CM 2

CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

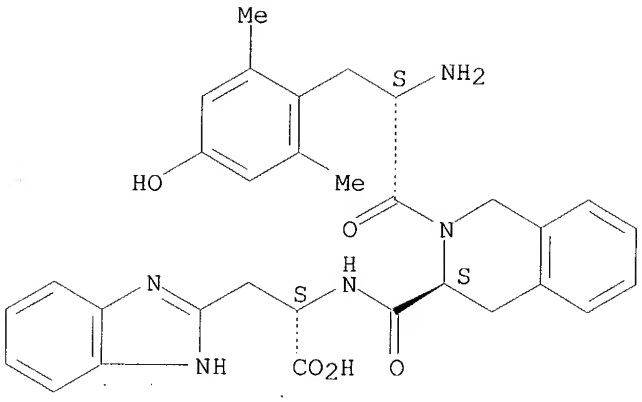
REFERENCE 1: 138:66167

L7 ANSWER 8 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 480446-54-6 REGISTRY
CN 1H-Benzimidazole-2-propanoic acid, α-[[[(3S)-2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinyl]carbonyl]amino]-, (αS)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H33 N5 O5 . 2 C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: PREP (Preparation); PRP (Properties)

CM 1

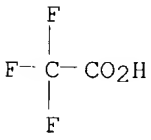
CRN 480446-45-5
CMF C31 H33 N5 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

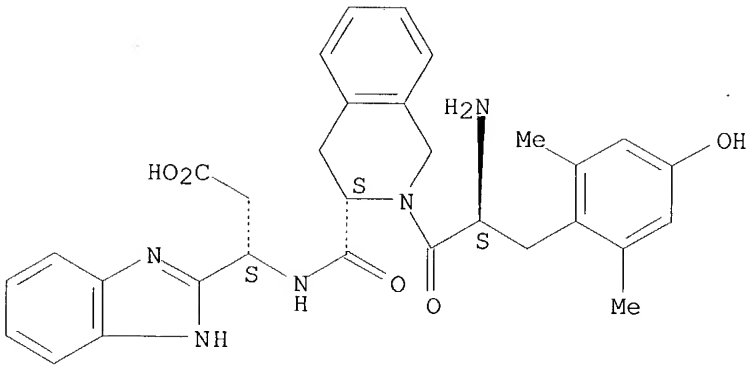
REFERENCE 1: 138:66167

L7 ANSWER 9 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 480446-51-3 REGISTRY
CN 1H-Benzimidazole-2-propanoic acid, β-[[[(3S)-2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinyl]carbonyl]amino]-, (βS)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H33 N5 O5 . 2 C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, CASREACT
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: PREP (Preparation); PRP (Properties)

CM 1

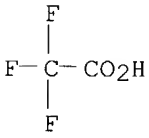
CRN 480446-44-4
CMF C31 H33 N5 O5

Absolute stereochemistry. Rotation (+).



CM 2

CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

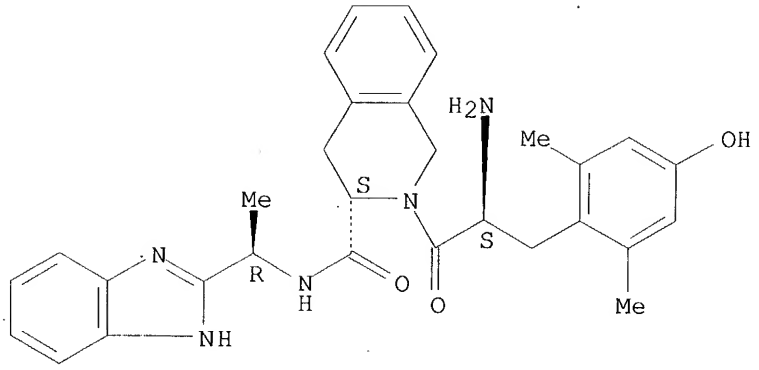
REFERENCE 1: 138:66167

L7 ANSWER 10 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 480446-50-2 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-N-[(1R)-1-(1H-benzimidazol-2-yl)ethyl]-1,2,3,4-tetrahydro-, (3S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H33 N5 O3 . 2 C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: PREP (Preparation); PRP (Properties)

CM 1

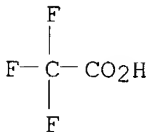
CRN 480446-47-7
CMF C30 H33 N5 O3

Absolute stereochemistry. Rotation (+).



CM 2

CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

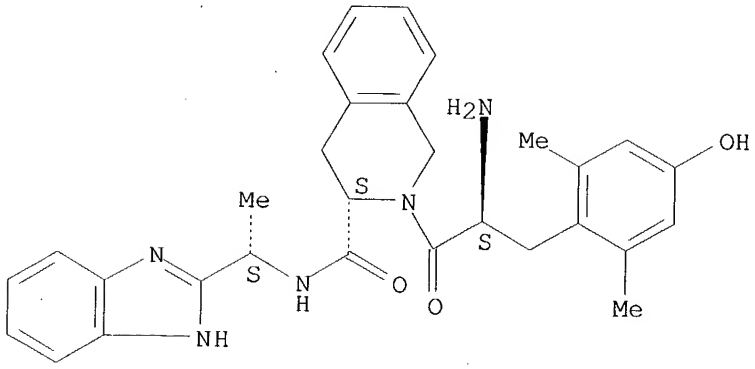
REFERENCE 1: 138:66167

L7 ANSWER 11 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 480446-49-9 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-N-[(1S)-1-(1H-benzimidazol-2-yl)ethyl]-1,2,3,4-tetrahydro-, (3S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H33 N5 O3 . 2 C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: PREP (Preparation); PRP (Properties)

CM 1

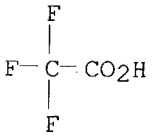
CRN 480446-43-3
CMF C30 H33 N5 O3

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

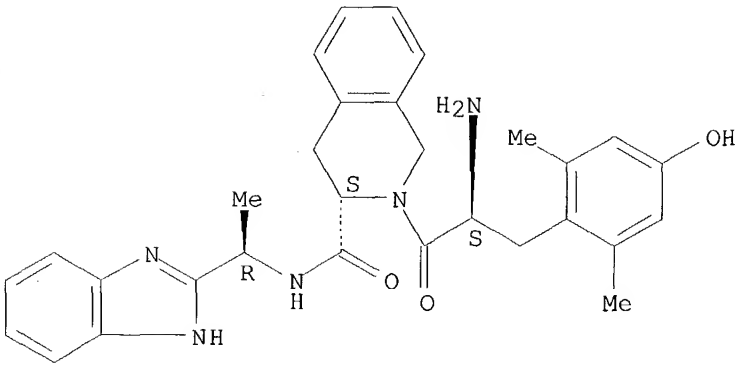


1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 138:66167

L7 ANSWER 12 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 480446-47-7 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-N-[(1R)-1-(1H-benzimidazol-2-yl)ethyl]-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H33 N5 O3
CI COM
SR CA
LC STN Files: CA, CAPLUS, CASREACT
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PRP (Properties)

Absolute stereochemistry. Rotation (+).



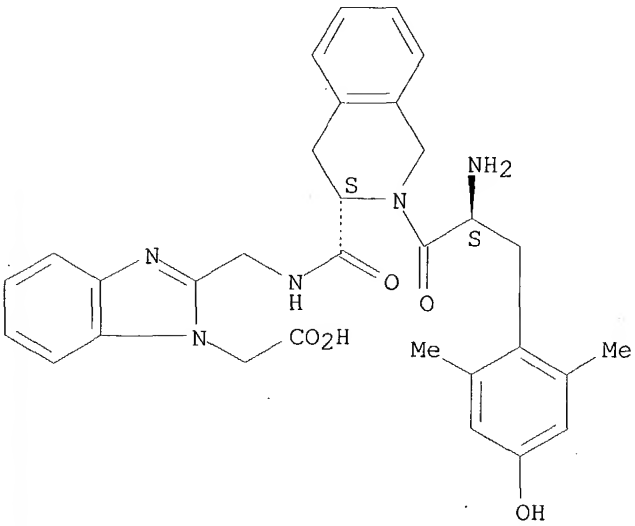
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 138:66167

L7 ANSWER 13 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 480446-46-6 REGISTRY
CN 1H-Benzimidazole-1-acetic acid, 2-[[[[(3S)-2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinyl]carbonyl]amino]methyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H33 N5 O5
CI COM
SR CA
LC STN Files: CA, CAPLUS, CASREACT
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PRP (Properties)

Absolute stereochemistry. Rotation (-).



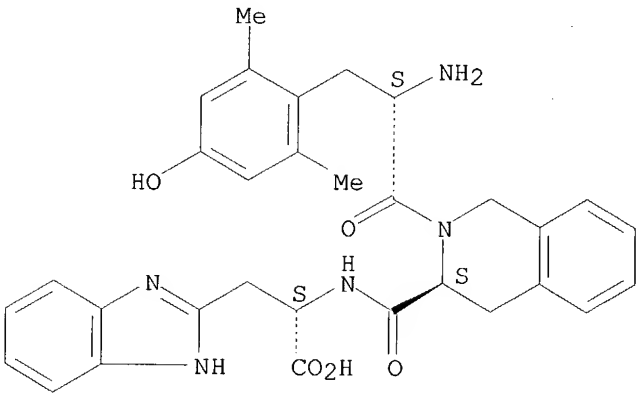
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 138:66167

L7 ANSWER 14 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 480446-45-5 REGISTRY
CN 1H-Benzimidazole-2-propanoic acid, α-[[[(3S)-2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinyl]carbonyl]amino]-, (αS)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H33 N5 O5
CI COM
SR CA
LC STN Files: CA, CAPLUS, CASREACT
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PRP (Properties)

Absolute stereochemistry.



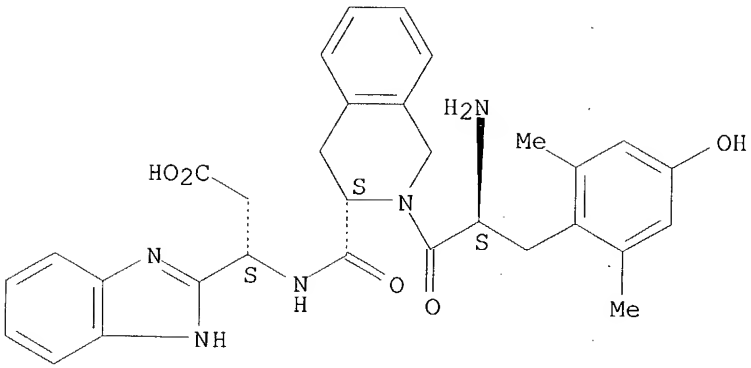

**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 138:66167

L7 ANSWER 15 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 480446-44-4 REGISTRY
CN 1H-Benzimidazole-2-propanoic acid, β-[[[(3S)-2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinyl]carbonyl]amino]-, (βS)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H33 N5 O5
CI COM
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PRP (Properties)

Absolute stereochemistry. Rotation (+).



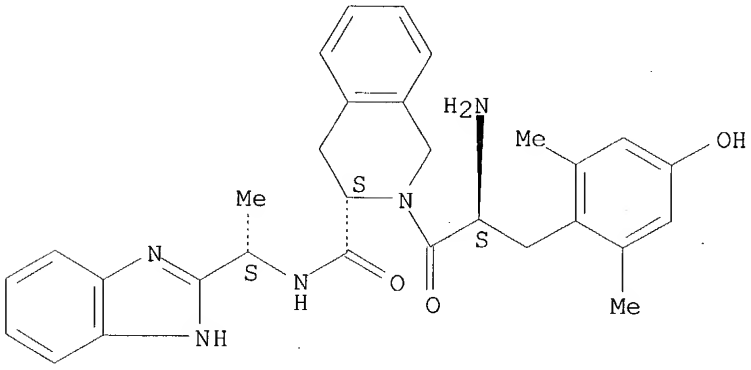
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 138:66167

L7 ANSWER 16 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 480446-43-3 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-N-[(1S)-1-(1H-benzimidazol-2-yl)ethyl]-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H33 N5 O3
CI COM
SR CA
LC STN Files: CA, CAPLUS, CASREACT
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PRP (Properties)

Absolute stereochemistry.

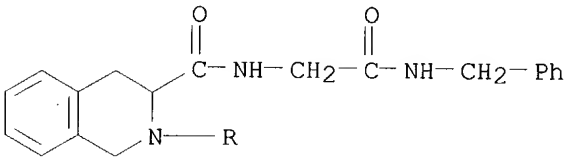


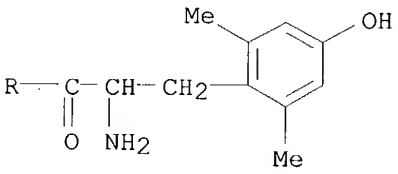
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 138:66167

L7 ANSWER 17 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 474015-63-9 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-[2-oxo-2-[(phenylmethyl)amino]ethyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C30 H34 N4 O4
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)



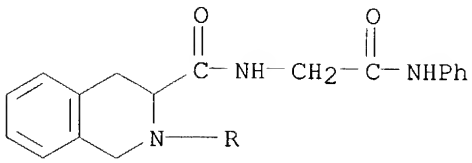


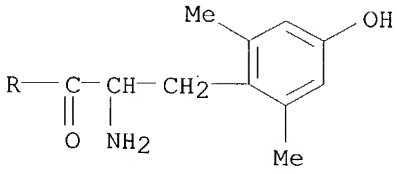
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:338140

L7 ANSWER 18 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 474015-57-1 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-[2-oxo-2-(phenylamino)ethyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C29 H32 N4 O4
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)



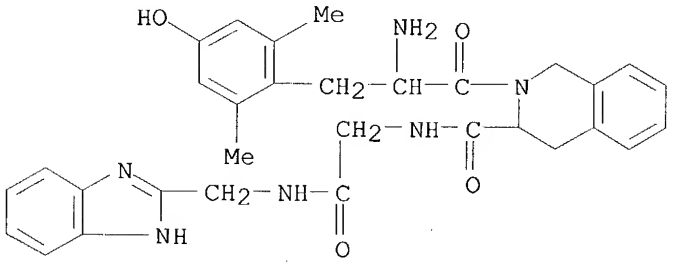


**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:338140

L7 ANSWER 19 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 474015-53-7 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-N-[2-[(1H-benzimidazol-2-ylmethyl)amino]-2-oxoethyl]-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C31 H34 N6 O4
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)



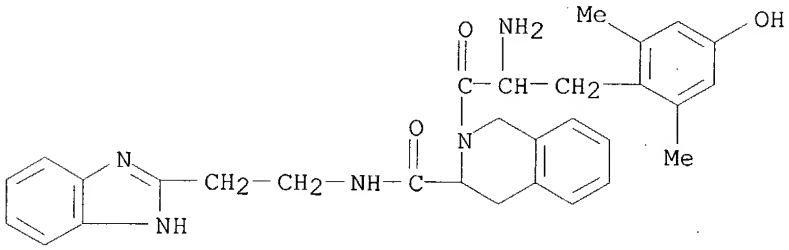
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:338140

L7 ANSWER 20 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 474015-50-4 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-

oxopropyl]-N-[2-(1H-benzimidazol-2-yl)ethyl]-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C30 H33 N5 O3
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

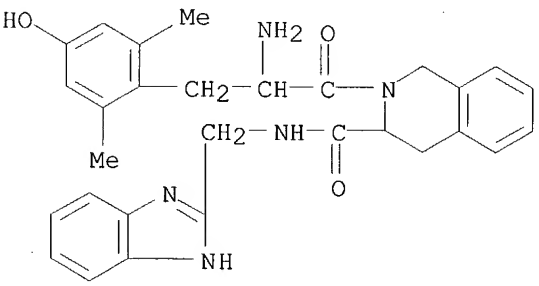


**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:338140

L7 ANSWER 21 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 474015-45-7 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-N-(1H-benzimidazol-2-ylmethyl)-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C29 H31 N5 O3
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

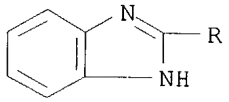


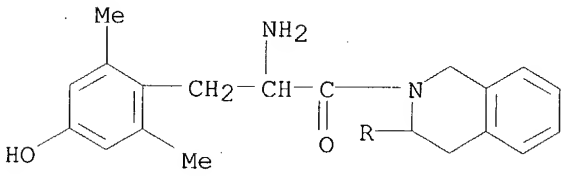
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:338140

L7 ANSWER 22 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 474015-40-2 REGISTRY
CN Isoquinoline, 2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-3-(1H-benzimidazol-2-yl)-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C27 H28 N4 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

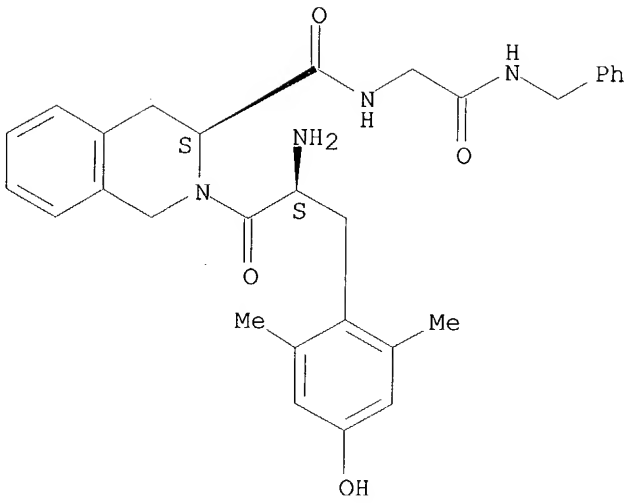
REFERENCE 1: 137:338140

L7 ANSWER 23 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 474013-89-3 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-[2-oxo-2-[(phenylmethyl)amino]ethyl]-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H34 N4 O4 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

CM 1

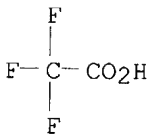
CRN 403652-14-2
CMF C30 H34 N4 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

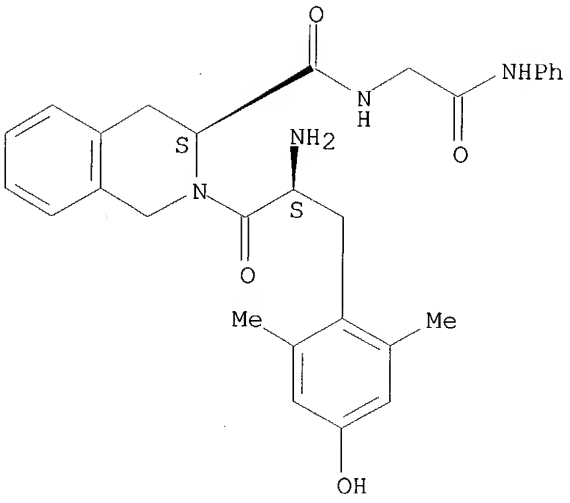
REFERENCE 1: 137:338140

L7 ANSWER 24 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 474013-86-0 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-[2-oxo-2-(phenylamino)ethyl]-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C29 H32 N4 O4 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

CM 1

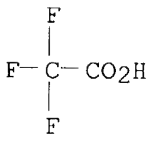
CRN 403652-13-1
CMF C29 H32 N4 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

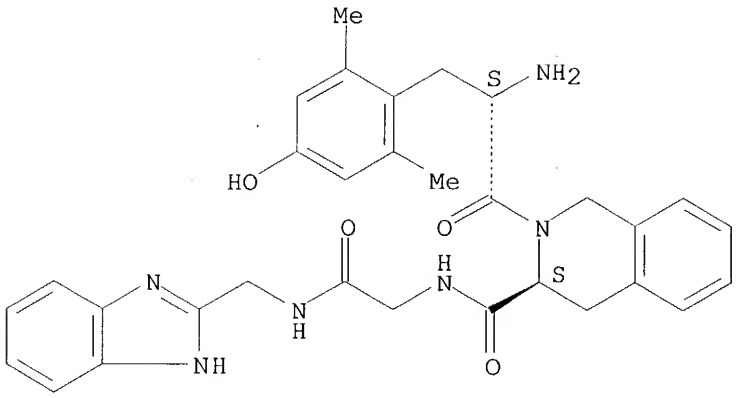
REFERENCE 1: 137:338140

L7 ANSWER 25 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 474013-84-8 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-N-[2-[(1H-benzimidazol-2-ylmethyl)amino]-2-oxoethyl]-1,2,3,4-tetrahydro-, (3S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H34 N6 O4 . 2 C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

CM 1

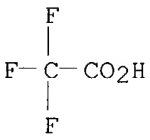
CRN 403652-12-0
CMF C31 H34 N6 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

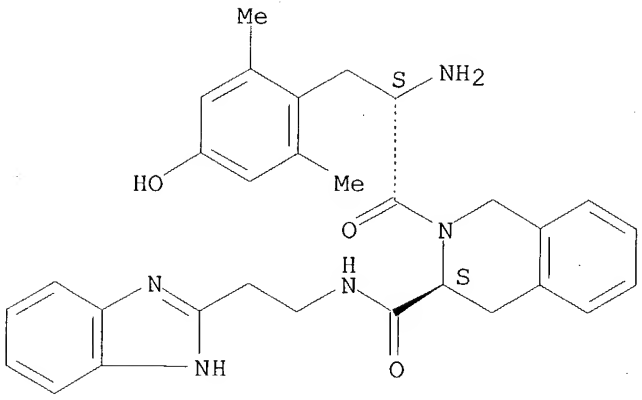
REFERENCE 1: 137:338140

L7 ANSWER 26 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 474013-82-6 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-N-[2-(1H-benzimidazol-2-yl)ethyl]-1,2,3,4-tetrahydro-, (3S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H33 N5 O3 . 2 C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

CM 1

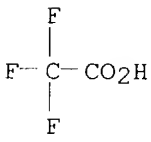
CRN 403652-11-9
CMF C30 H33 N5 O3

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

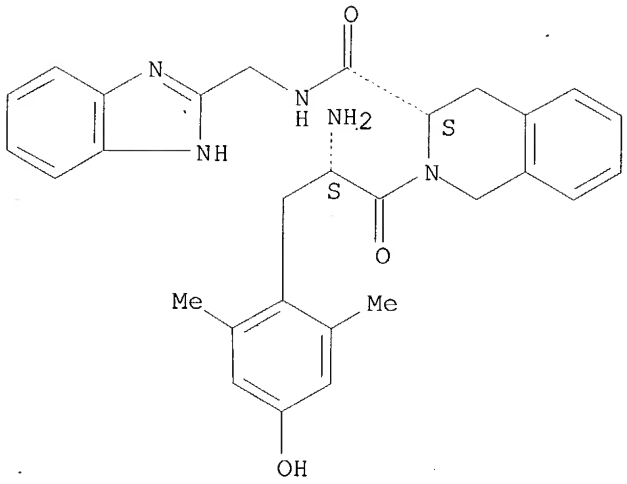
REFERENCE 1: 137:338140

L7 ANSWER 27 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 474013-80-4 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-N-(1H-benzimidazol-2-ylmethyl)-1,2,3,4-tetrahydro-, (3S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C29 H31 N5 O3 . 2 C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

CM 1

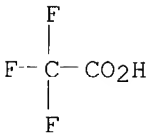
CRN 403652-10-8
CMF C29 H31 N5 O3

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

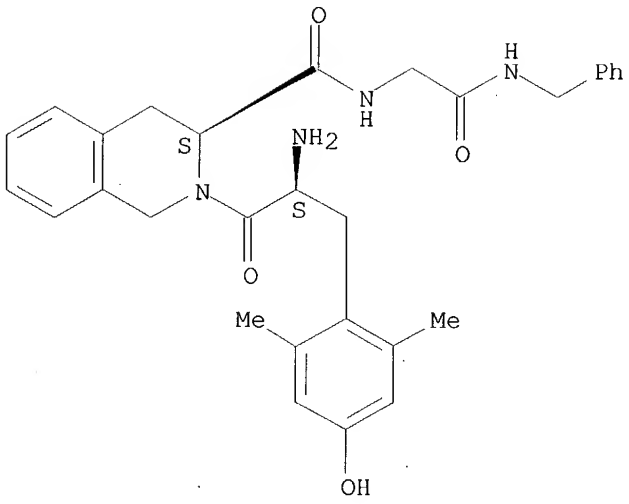


1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:338140

L7 ANSWER 28 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 403652-14-2 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-[2-oxo-2-[(phenylmethyl)amino]ethyl]-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H34 N4 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Conference; Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

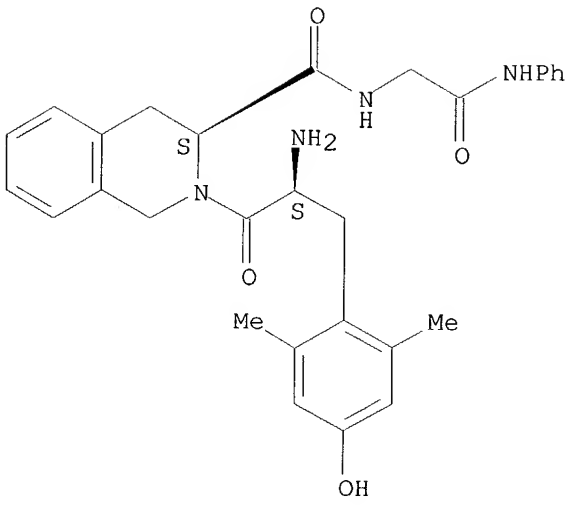
REFERENCE 1: 140:263738

REFERENCE 2: 138:338458

REFERENCE 3: 136:226323

L7 ANSWER 29 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 403652-13-1 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-[2-oxo-2-(phenylamino)ethyl]-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C29 H32 N4 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Conference; Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

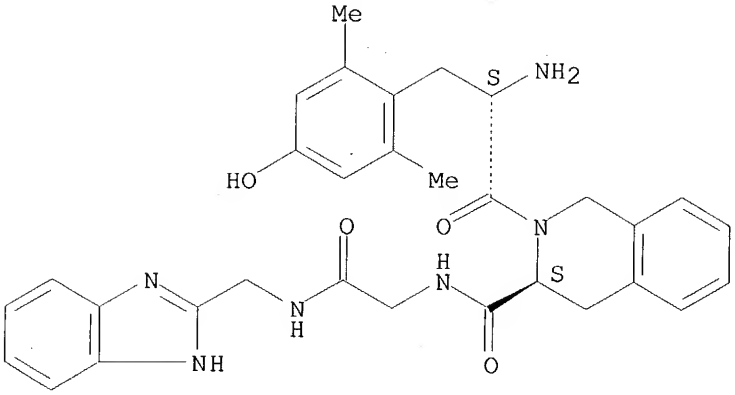
REFERENCE 1: 140:263738

REFERENCE 2: 138:338458

REFERENCE 3: 136:226323

L7 ANSWER 30 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 403652-12-0 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-N-[2-[(1H-benzimidazol-2-ylmethyl)amino]-2-oxoethyl]-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H34 N6 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Conference; Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

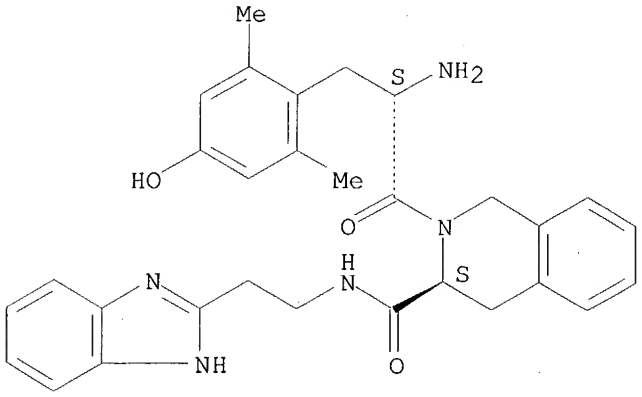
REFERENCE 1: 140:263738

REFERENCE 2: 138:338458

REFERENCE 3: 136:226323

L7 ANSWER 31 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 403652-11-9 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-N-[2-(1H-benzimidazol-2-yl)ethyl]-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H33 N5 O3
CI COM
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Conference; Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PRP (Properties); USES (Uses)

Absolute stereochemistry.



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:263738

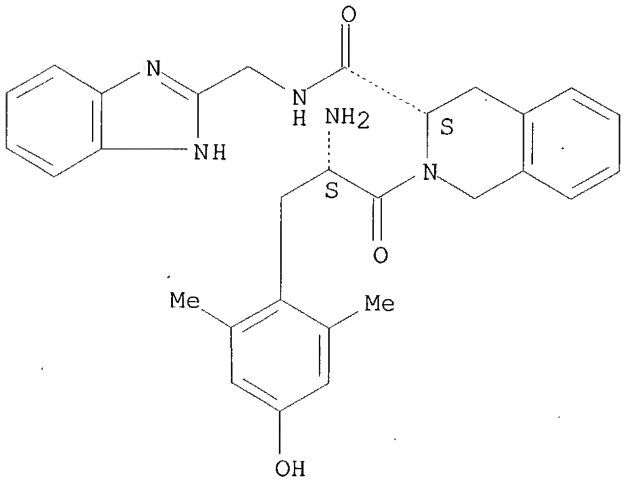
REFERENCE 2: 138:338458

REFERENCE 3: 138:66167

REFERENCE 4: 136:226323

L7 ANSWER 32 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 403652-10-8 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-N-(1H-benzimidazol-2-ylmethyl)-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C29 H31 N5 O3
CI COM
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Conference; Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PRP (Properties); USES (Uses)

Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:263738

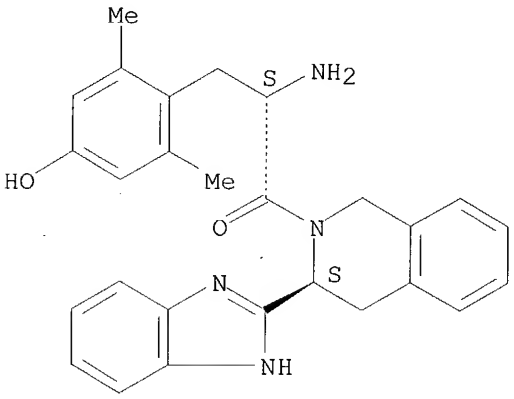
REFERENCE 2: 138:338458

REFERENCE 3: 138:66167

REFERENCE 4: 136:226323

L7 ANSWER 33 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 403652-09-5 REGISTRY
CN Isoquinoline, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-3-(1H-benzimidazol-2-yl)-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H28 N4 O2
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

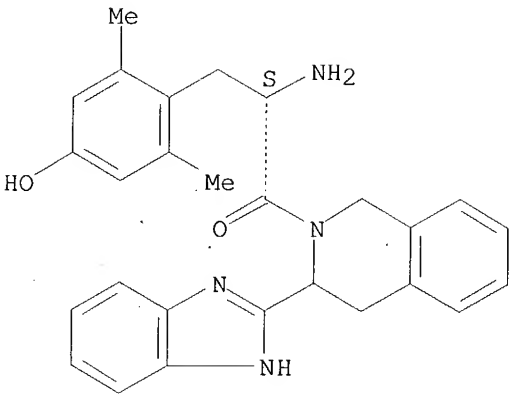
2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:263738

REFERENCE 2: 136:226323

L7 ANSWER 34 OF 34 REGISTRY COPYRIGHT 2004 ACS on STN
RN 314756-49-5 REGISTRY
CN Isoquinoline, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-3-(1H-benzimidazol-2-yl)-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H28 N4 O2
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process)

Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 134:66089

=> □

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 16:44:34 ON 18 JUN 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.


FILE COVERS 1907 - 18 Jun 2004 VOL 140 ISS 26
FILE LAST UPDATED: 17 Jun 2004 (20040617/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=>
=>

=> => d stat que l15 nos
L1 STR
L5 326 SEA FILE=REGISTRY SSS FUL L1
L6 STR
L7 34 SEA FILE=REGISTRY SUB=L5 SSS FUL L6
L8 7 SEA FILE=HCAPLUS ABB=ON PLU=ON L7
L10 292 SEA FILE=REGISTRY ABB=ON PLU=ON L5 NOT L7
L13 53 SEA FILE=HCAPLUS ABB=ON PLU=ON L10

L14 46 SEA FILE=HCAPLUS ABB=ON PLU=ON L13 NOT L8
L15 34 SEA FILE=HCAPLUS ABB=ON PLU=ON L14 AND PD<= MARCH 24, 2000

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=> d ibib abs hitrn l15 1-34

L15 ANSWER 1 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:894623 HCAPLUS
DOCUMENT NUMBER: 135:40848
TITLE: Opioid dipeptide derivatives with a mixed μ agonist/δ antagonist, partial μ agonist/δ antagonist or μ agonist/partial δ agonist profile
AUTHOR(S): Schiller, Peter W.; Weltrowska, Grazyna; Nguyen, Thi M. -D.; Wilkes, Brian C.; Lemieux, Carole; Chung, Nga N.
CORPORATE SOURCE: Laboratory of Chemical Biology and Peptide Research, Clinical Research Institute of Montreal, Montreal, QC, H2W 1R7, Can.
SOURCE: Peptides for the New Millennium, Proceedings of the American Peptide Symposium, 16th, Minneapolis, MN, United States, June 26-July 1, 1999 (**2000**), Meeting Date 1999, 229-230. Editor(s): Fields, Gregg B.; Tam, James P.; Barany, George. Kluwer Academic Publishers: Dordrecht, Neth.
CODEN: 69ATHX
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Opioid compds. with a mixed μ agonist/δ antagonist profile are expected to be analgesics with low propensity to produce tolerance and dependence. The first fully characterized mixed μ agonist/δ antagonist was the pseudotetrapeptide H-Dmt-Tic[CH2NH]Phe-Phe-NH2; Dmt = 2',6'-dimethyltyrosine which produced a potent analgesic effect, no dependence and less tolerance than morphine. In an effort to develop mixed μ agonist/δ antagonists of lower mol. weight capable of crossing the blood-brain barrier, dipeptide derivs. of the general formula H-Xxx-Tic-NH-R, where Xxx is tyrosine or a tyrosine analog and R represents an aralkyl or alkyl substituent, were synthesized. The dipeptide derivs. were synthesized in solution using the mixed anhydride method. In vitro opioid agonist or antagonist activities of the resulting compds. were determined in the μ receptor-representative guine pig ileum assay and in the δ receptor-representative mouse vas deferens assay, and their μ, δ, κ opioid receptor affinities were measured in binding assays based on the displacement of μ-, δ- and κ-selective radioligands from rat or guinea pig brain membrane binding sites.
IT **173927-99-6P 209786-77-6P 344615-76-5P**
**344615-77-6P 344615-78-7P 344615-79-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(opioid dipeptide derivs. with mixed μ agonist/δ antagonist, partial μ agonist/δ antagonist or μ agonist/partial δ agonist profile)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:853641 HCAPLUS
DOCUMENT NUMBER: 134:216792

TITLE: Assessment of substitution in the second pharmacophore of Dmt-Tic analogues
AUTHOR(S): Santagada, V.; Balboni, G.; Caliendo, G.; Guerrini, R.; Salvadori, S.; Bianchi, C.; Bryant, S. D.; Lazarus, L. H.
CORPORATE SOURCE: Medicinal Chemistry and Toxicology, University of Naples, Naples, I-80134, Italy
SOURCE: Bioorganic & Medicinal Chemistry Letters (2000), 10(24), 2745-2748
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The Dmt-Tic pharmacophore exhibits potent δ-opioid receptor antagonism. Analogs with substitutions in the second pharmacophore with or without a COOH function were synthesized: several had high δ affinity, but exhibited low to non-selectivity toward μ receptors similar to H-Dmt-Tic-amide and H-Dmt-Tic-ol. Functional bioactivity indicated high δ antagonism (pA2 7.4-7.9) and modest μ agonism, pEC50 (6.1-6.3), but with Emax values analogous to dermorphin. These Dmt-Tic analogs with mixed δ antagonist/μ agonist properties would appear to be better candidates as analgesics than pure μ agonists.

IT **329320-06-1 329320-07-2**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(opioid receptor binding activity of dimethyltyrosine isoquinolinecarboxylates)

IT **329319-97-3P 329320-03-8P 329320-04-9P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(opioid receptor binding activity of dimethyltyrosine isoquinolinecarboxylates)

IT **329319-96-2P 329319-98-4P 329319-99-5P 329320-00-5P 329320-01-6P 329320-02-7P 329320-05-0P**
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(opioid receptor binding activity of dimethyltyrosine isoquinolinecarboxylates)

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 3 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:677175 HCAPLUS
DOCUMENT NUMBER: 134:51294
TITLE: Inverse agonism by Dmt-Tic analogues and HS 378, a naltrindole analogue
AUTHOR(S): Labarre, M.; Butterworth, J.; St-Onge, S.; Payza, K.; Schmidhammer, H.; Salvadori, S.; Balboni, G.; Guerrini, R.; Bryant, S. D.; Lazarus, L. H.
CORPORATE SOURCE: Department of Pharmacology, AstraZeneca R&D Montreal, St-Laurent, QC, H4S 1Z9, Can.
SOURCE: European Journal of Pharmacology (2000), 406(1), R1-R3
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The potent δ-opioid receptor antagonist H-2',6-l-tyrosine(Dmt)-

1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic-OH) exhibited partial inverse agonism (EC50=6.35 nM, Emax=-18.87%) for [35S]GTPγS binding and H-Dmt-Tic-NH2 was a neutral antagonist (no effect up to 30 μM). In contrast N,N(CH3)2-Dmt-Tic-NH2 was a full inverse agonist (EC50=2.66 nM, Emax=-35.95%) similar to ICI 174864 ([N,N-diallyl-Tyr1,Aib2,3,Leu5]enkephaline) but with a 3.5-fold higher EC50. In comparison, naltrindole was a neutral antagonist while its analog HS 378 was a partial inverse agonist (Emax=-12.99%).

IT **172262-39-4 172262-40-7 178951-50-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inverse agonism by Dmt-Tic analogs and HS 378)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 4 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:288696 HCAPLUS
DOCUMENT NUMBER: 133:12871
TITLE: Opioid peptide analogs containing 2'-hydroxy,6'-methyltyrosine in place of Tyr1 display greatly enhanced δ antagonist potency but unchanged μ agonist potency
AUTHOR(S): Berezowska, Irena; Lemieux, Carole; Nguyen, Thi M. -D.; Chung, Nga N.; Schiller, Peter W.
CORPORATE SOURCE: Clinical Research Institute of Montreal, Montreal, QC, H2W 1R7, Can.
SOURCE: Peptides 1998, Proceedings of the European Peptide Symposium, 25th, Budapest, Aug. 30-Sept. 4, 1998 (**1999**), Meeting Date 1998, 718-719. Editor(s): Bajusz, Sandor; Hudecz, Ferenc. Akademiai Kiado: Budapest, Hung.
CODEN: 68WKAY
DOCUMENT TYPE: Conference
LANGUAGE: English

AB The authors report the syntheses and in vitro opioid activity profiles of the Hmt1-analogs of the δ antagonists TIP (H-Tyr-Tic-Phe-OH) and TIPP (H-Tyr-Tic-Phe-Phe-OH) and of the μ agonists TAPP (H-Tyr-D-Ala-Phe-Phe-NH2) and DALDA (H-Tyr-D-Arg-Phe-Lys-NH2). In vitro opioid activities of the compds. were determined in the μ-receptor-representative guinea pig ileum assay and in the δ receptor-representative mouse vas deferens (MVD) assay, and their μ and δ receptor affinities were measured in binding assays based on displacement of [3H]DAMGO and [3H]DSLET, resp., from rat brain membrane binding sites. The tripeptide H-Hmt-Tic-Phe-OH was an about 15 times more potent δ antagonist against the δ agonist DPDPE than its parent TIP, showing δ antagonist potency (MVD) and δ receptor binding affinity in the subnanomolar range. Furthermore, this compound showed greatly improved δ receptor selectivity as compared to TIP. The Hmt1-analog of the tetrapeptide TIPP, H-Hmt-Tic-Phe-Phe-OH, displayed very high δ antagonist potency in the MVD assay, comparable to that of H-Dmt-Tic-Phe-Phe-OH. In the binding assays, it showed slightly higher δ receptor affinity than H-Dmt-Tic-Phe-Phe-OH and 20-fold higher δ selectivity. Thus, [Hmt1]TIPP ranks among the most potent and most specific δ opioid antagonists reported to date. Substitution of Hmt for Tyr1 in the μ agonist peptides TAPP and DALDA resulted in μ-agonist potencies comparable to those of their resp. parent peptides,. In conclusion, replacement of Tyr1 in opioid peptides with Hmt produced a potency increase in the case of the δ antagonists but not in the case of the μ agonists.

IT **156219-37-3**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)

(opioid peptide analogs δ antagonist and μ agonist activity in relation to structure)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 5 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:288655 HCAPLUS
DOCUMENT NUMBER: 133:99680
TITLE: Tritium labelling of neuropeptides
AUTHOR(S): Toth, Geza; Farkas, Judit; Kertesz, Istvan; Tomboly, Csaba; Darula, Zsuzsanna; Peter, Antal
CORPORATE SOURCE: Institute of Biochemistry, Biological Research Centre, Hungarian Academy of Sciences, Szeged, H-6701, Hung.
SOURCE: Peptides 1998, Proceedings of the European Peptide Symposium, 25th, Budapest, Aug. 30-Sept. 4, 1998 (**1999**), Meeting Date 1998, 636-637. Editor(s): Bajusz, Sandor; Hudecz, Ferenc. Akademiai Kiado: Budapest, Hung.
CODEN: 68WKAY
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A report from a symposium presenting examples on the tritiation of labeled neuropeptides from synthetic precursor peptides. Catalytic dehalogenation with tritium gas produces radioactive peptides with high specific radioactivity, and with this method, the following new opioid peptides were radiolabeled: endomorphin II (μ agonist), N,N-(CH3)2-Dmt-Tic (δ antagonist), D-Ala2-D-Nle5-Met-enkephalin-Arg-Phe (κ2 agonist), V-V-hemorphin 7 (Val-Val-Tyr-Pro-Trp-Thr-Gln-Arg-Phe) and dermorphin (μ agonist). Precursor peptides were synthesized by solid phase peptide synthesis using the Boc method and the crude peptides were purified on RP-HPLC. The tritiation reaction was carried out on Pd/BaSO4 catalyst with triethylamine to bind the proceeded acid in DMF as solvent with carrier free tritium gas. The crude radiolabeled peptides were purified by RP-HPLC using a radiodetector. Specific radioactivity of the tritiated peptides was then calculated from the radioactivity and the amount of the peptide. Finally, the tritiated peptides were stored as ethanolic solns. in liquid nitrogen and the stability of the ligands during storage and under binding conditions was investigated using rat brain membrane and HPLC.
IT **220045-96-5P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(opioid neuropeptide labeling with tritium and catalytic halogenation using synthetic precursor ligands)
IT **220045-93-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(opioid neuropeptide labeling with tritium and catalytic halogenation using synthetic precursor ligands)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 6 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:94013 HCAPLUS
DOCUMENT NUMBER: 132:245845
TITLE: Novel Dmt-Tic dipeptide analogues as selective delta-opioid receptor antagonists
AUTHOR(S): Page, D.; McClory, A.; Mischki, T.; Schmidt, R.; Butterworth, J.; St-Onge, S.; Labarre, M.; Payza, K.; Brown, W.
CORPORATE SOURCE: Department of Chemistry, AstraZeneca R and D Montreal, Saint-Laurent, QC, H4S 1Z9, Can.
SOURCE: Bioorganic & Medicinal Chemistry Letters (**2000**

), 10(2), 167-170
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of Dmt-Tic analogs with substitution on the Tic aromatic ring has been synthesized and evaluated for opioid receptor affinity and activation. Incorporation of large hydrophobic groups at position 7 of Tic did not greatly alter the δ opioid receptor binding affinities of the dipeptides whereas substitution at position 6 substantially diminished their affinity. These modified Dmt-Tic peptides showed binding affinities as low as 2.5 nM with ≤500-fold selectivity for the δ vs. μ opioid receptor and proved to be δ receptor antagonists.

IT **262616-34-2P 262616-35-3P 262616-36-4P**
**262616-37-5P 262616-38-6P 262616-39-7P**
**262616-40-0P 262616-41-1P 262616-42-2P**
**262616-43-3P 262616-44-4P 262616-45-5P**
**262616-46-6P 262616-47-7P 262616-48-8P**
**262616-49-9P 262616-50-2P 262616-51-3P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(novel Dmt-Tic dipeptide analogs as selective delta-opioid receptor antagonists)

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 7 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:715597 HCAPLUS
DOCUMENT NUMBER: 132:73213
TITLE: Further Studies on the Dmt-Tic Pharmacophore: Hydrophobic Substituents at the C-Terminus Endow δ Antagonists To Manifest μ Agonism or μ Antagonism
AUTHOR(S): Salvadori, Severo; Guerrini, Remo; Balboni, Gianfranco; Bianchi, Clementina; Bryant, Sharon D.; Cooper, Peter S.; Lazarus, Lawrence H.
CORPORATE SOURCE: Department of Pharmaceutical Science and Biotechnology Center, University of Ferrara, Ferrara, I-441000, Italy
SOURCE: Journal of Medicinal Chemistry (**1999**), 42(24), 5010-5019
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
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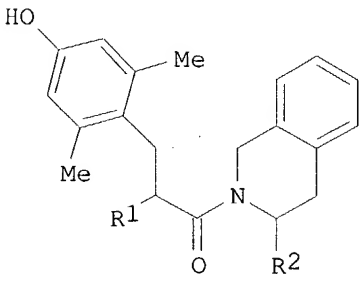



I

AB Twenty N- and/or C-modified Dmt-Tic analogs (I; R1=NH2,CH2NH2,heterocyclics; R2=CH2COOH, COOH, etc.) yielded similar Ki values with either [3H]DPDPE (δ1 agonist) or [3H]N,N(Me)2-Dmt-Tic-OH (δ antagonist). N-Methylation enhanced δ antagonism while N-piperidine-1-yl, N-pyrrolidine-1-yl, and N-pyrrole-1-yl were detrimental. Dmt-Tic-X (X = -NHNH2, -NHCH3, -NH-1-adamantyl, -NH-tBu, -NH-5-tetrazolyl) had high δ affinities (Ki = 0.16 to 1 nM) with variable μ affinities to yield nonselective or weakly μ-selective analogs. N,N-(Me)2Dmt-Tic-NH-1-adamantane exhibited dual δ and μ receptor affinities (Kiδ = 0.16 nM and Kiμ = 1.12 nM) and potent δ antagonism (pA2 = 9.06) with μ agonism (IC50 = 16 nM). H-Dmt-βHTic-OH (methylene bridge between Cα of Tic and carboxylate function) yielded a biostable peptide with high δ affinity (Ki = 0.85 nM) and δ antagonism (pA2 = 8.85) without μ bioactivity. Dmt-Tic-Ala-X (X = -NHCH3, -OCH3, -NH-1-adamantyl, -NHtBu) exhibited high δ affinities (Ki = 0.06 to 0.2 nM) and elevated μ affinities (Ki = 2.5 to 11 nM), but only H-Dmt-Tic-Ala-NH-1-adamantane and H-Dmt-Tic-Ala-NHtBu yielded δ receptor antagonism (pA2 = 9.29 and 9.16, resp.). Thus, Dmt-Tic with hydrophobic C-terminal substituents enhanced μ affinity to provide δ antagonists with dual receptor affinities and bifunctional activity.

IT **172262-39-4P 172262-40-7P 172262-47-4P**
**172262-48-5P 178951-49-0P 194857-80-2P**
**254101-66-1P 254101-75-2P 254101-77-4P**
**254101-78-5P 254101-80-9P 254101-82-1P**
**254101-84-3P 254101-86-5P 254101-88-7P**
**254101-90-1P 254101-92-3P 254101-94-5P**
**254101-96-7P 254101-98-9P 254102-00-6P**
**254102-01-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(studies on opioid pharmacophore, hydrophobic substituents at C-terminus endow δ antagonists to manifest μ agonism or μ antagonism)

IT **189093-95-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(studies on opioid pharmacophore, hydrophobic substituents at C-terminus endow δ antagonists to manifest μ agonism or μ antagonism)

IT **254102-02-8P 254102-03-9P 254102-06-2P**
**254102-07-3P 254102-09-5P 254102-11-9P**
**254102-12-0P 254102-13-1P 254102-17-5P**
**254102-21-1P 254102-25-5P 254102-26-6P**
**254102-27-7P 254102-28-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(studies on opioid pharmacophore, hydrophobic substituents at C-terminus endow δ antagonists to manifest μ agonism or μ antagonism)

REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 8 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:667719 HCAPLUS
DOCUMENT NUMBER: 131:347049
TITLE: (2S,3R)TMT-L-Tic-OH is a potent inverse agonist at the human δ-opioid receptor
AUTHOR(S): Hosohata, Keiko; Burkey, Thomas H.; Alfaro-Lopez, Josua; Hruby, Victor J.; Roeske, William R.; Yamamura, Henry I.
CORPORATE SOURCE: Departments of Pharmacology, Biochemistry, Psychiatry and Chemistry, University of Arizona, Tucson, AZ,

85724, USA
SOURCE: European Journal of Pharmacology (**1999**), 380(1), R9-R10
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We examined the pharmacol. effect of β-methyl-2',6'-dimethyltyrosine-L-tetrahydroisoquinoline-3-carboxylic acid ((2S,3R)TMT-L-Tic-OH) on G protein activation in membranes prepared from Chinese Hamster Ovary cells transfected with cDNA of the human δ-opioid receptor. (2S,3R)TMT-L-Tic-OH inhibited G protein activation to 58% of basal with an EC50 of 0.72 nM as determined by [35S]GTPγS binding. These findings suggest that (2S,3R)TMT-L-Tic-OH is a highly potent inverse agonist at the human δ-opioid receptor.

IT **250331-76-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
((2S,3R)TMT-L-Tic-OH is a potent inverse agonist at the human δ-opioid receptor)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 9 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:484863 HCAPLUS
DOCUMENT NUMBER: 131:266894
TITLE: The Opioid μ Agonist/δ Antagonist DIPP-NH2[Ψ] Produces a Potent Analgesic Effect, No Physical Dependence, and Less Tolerance than Morphine in Rats
AUTHOR(S): Schiller, Peter W.; Fundytus, Marian E.; Merovitz, Lisa; Weltrowska, Grazyna; Nguyen, Thi M.-D.; Lemieux, Carole; Chung, Nga N.; Coderre, Terence J.
CORPORATE SOURCE: Laboratory of Chemical Biology and Peptide Research and Pain Mechanisms Laboratory, Clinical Research Institute of Montreal, Montreal, QC, H2W 1R7, Can.
SOURCE: Journal of Medicinal Chemistry (**1999**), 42(18), 3520-3526
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Opioid compds. with mixed μ agonist/δ antagonist properties are expected to be analgesics with low propensity to produce tolerance and dependence. In an effort to strengthen the μ agonist component of the mixed μ agonist/δ antagonist H-Tyr-Tic-Phe-Phe-NH2 (TIPP-NH2), analogs containing structurally modified tyrosine residues in place of Tyr1 were synthesized. Among the prepared compds., H-Dmt-Tic-Phe-Phe-NH2 (DIPP-NH2; Dmt = 2',6'-dimethyltyrosine) and H-Dmt-TicΨ[CH2NH]Phe-Phe-NH2 (DIPP-NH2[Ψ]) retained a mixed μ agonist/δ antagonist profile, as determined in the guinea pig ileum and mouse vas deferens assays, whereas H-Tmt-Tic-Phe-Phe-NH2 (Tmt = N,2',6'-trimethyltyrosine) was a partial μ agonist/δ antagonist and H-Tmt-TicΨ[CH2NH]Phe-Phe-NH2 was a μ antagonist/δ antagonist. DIPP-NH2[Ψ] showed binding affinities in the subnanomolar range for both μ and δ receptors in the rat brain membrane binding assays, thus representing the first example of a balanced μ agonist/δ antagonist with high potency. In the rat tail flick test, DIPP-NH2[Ψ] given icv produced a potent analgesic effect (ED50 = 0.04 μg), being about 3 times more potent than morphine (ED50 = 0.11 μg). It produced less acute tolerance than morphine but still a certain level of chronic tolerance. Unlike morphine, DIPP-NH2[Ψ] produced no phys. dependence whatsoever upon chronic administration at high doses (≤4.5 μg/h) over a

7-day period. In conclusion, DIPP-NH2[Ψ] fulfills to a large extent the expectations based on the mixed μ agonist/δ antagonist concept with regard to analgesic activity and the development of tolerance and dependence.

IT **160429-67-4P 160429-68-5P 245538-28-7P 245538-29-8P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(opioid μ agonist/δ antagonist DIPP-NH2[Ψ] produces a potent analgesic effect and No phys. dependence and less tolerance than morphine in Rats in relation to structure)

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 10 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:410445 HCAPLUS
DOCUMENT NUMBER: 131:214535
TITLE: Tritiation of delta opioid-receptor selective antagonist dipeptide ligands with extraordinary affinity containing 2',6'-dimethyltyrosine
AUTHOR(S): Kertesz, I.; Toth, G.; Balboni, G.; Guerrini, R.; Salvadori, S.
CORPORATE SOURCE: Institute of Biochemistry, Biological Research Centre of the Hungarian Academy of Sciences, Szeged, H-6701, Hung.
SOURCE: Czechoslovak Journal of Physics (**1999**), 49(Suppl. 1, Pt. 2, 13th Radiochemical Conference, 1998), 887-892
CODEN: CZYPAO; ISSN: 0011-4626
PUBLISHER: Institute of Physics, Academy of Sciences of the Czech Republic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recently a new class of δ opioid antagonists has been discovered by using Tyr1-Tic2 sequence. The substitution of Tyr1 by Dmt (Dmt = 2',6'-dimethyltyrosine) resulted in a new analog H-Dmt-Tic-OH with enhanced affinity and selectivity. Peptides containing Tic at position 2 undergo spontaneous diketopiperazine formation in some solvents, and thus, loosing some of their binding ability. To avoid this unwanted side reaction, the authors synthesized the N,N-di-Me analog [N,N(Me)2Dmt-Tic-OH], and it was more stable under storage conditions, but its δ affinity declined moderately. On this basis, the authors prepared the diiodinated analogs of these dipeptides. Catalytic dehalotritiation of precursors resulted in tritiated peptides. High specific radioactivity, 44.67 Ci/mmol with H-[3H2]Dmt-Tic-OH and 59.88 Ci/mmol with N,N(Me)2[3H2]Dmt-Tic-OH were achieved.

IT **220045-95-4P 220045-96-5P**
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(preparation of tritiated 2',6'-dimethyltyrosyl dipeptides as antagonists of δ-opioid receptor)

IT **172262-39-4 178951-49-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of tritiated 2',6'-dimethyltyrosyl dipeptides as antagonists of δ-opioid receptor)

IT **220045-90-9P 220045-93-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of tritiated 2',6'-dimethyltyrosyl dipeptides as antagonists of δ-opioid receptor)

IT **220045-92-1P 220045-94-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of tritiated 2',6'-dimethyltyrosyl dipeptides as antagonists of δ-opioid receptor)
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 11 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:396671 HCAPLUS
DOCUMENT NUMBER: 131:200061
TITLE: Generation of new Dmt-Tic δ opioid antagonists: N-alkylation
AUTHOR(S): Lazarus, Lawrence H.; Salvadori, Severo; Balboni, Gianfranco; Guerrini, Remo; Bianchi, Clementina; Cooper, Peter S.; Bryant, Sharon D.
CORPORATE SOURCE: NIEHS, Research Triangle Park, NC, 27707, USA
SOURCE: Peptides: Frontiers of Peptide Science, Proceedings of the American Peptide Symposium, 15th, Nashville, June 14-19, 1997 (**1999**), Meeting Date 1997, 603-604. Editor(s): Tam, James P.; Kaumaya, Pravin T. P. Kluwer: Dordrecht, Neth.
CODEN: 67UCAR
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A symposium with seven refs. A discussion of the opioid antagonist properties of N-alkylated analogs of Tyr-Tic peptide was given.
IT **178951-49-0 178951-50-3 178951-51-4**
**178951-52-5 179091-74-8 194857-63-1**
**194857-70-0 194857-73-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(biol. activity of as δ opioid antagonists prepared via N-alkylation of Dmt-Tic peptide analogs)
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 12 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:396632 HCAPLUS
DOCUMENT NUMBER: 131:208606
TITLE: A new class of dipeptide derivatives that are potent and selective δ opioid agonists
AUTHOR(S): Schiller, P. W.; Weltrowska, G.; Berezowska, I.; Lemieux, C.; Chung, N. N.; Carpenter, K. A.; Wilkes, B. C.
CORPORATE SOURCE: Clinical Research Institute of Montreal, Montreal, QC, H2W 1R7, Can.
SOURCE: Peptides: Frontiers of Peptide Science, Proceedings of the American Peptide Symposium, 15th, Nashville, June 14-19, 1997 (**1999**), Meeting Date 1997, 514-516. Editor(s): Tam, James P.; Kaumaya, Pravin T. P. Kluwer: Dordrecht, Neth.
CODEN: 67UCAR
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A new class of potent and selective δ-opioid agonists has been developed by alteration of dipeptides having the general formula H-Tyr-Tic-NH-(CH2)n-Ph. Structure-activity data are presented for 18 dipeptides (displacement of DAMGO vs. DSLET from rat brain membrane binding sites).
IT **209786-77-6 209786-79-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dipeptide derivs. that are potent and selective δ opioid agonists)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 13 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:1815 HCAPLUS
DOCUMENT NUMBER: 130:139633
TITLE: Synthesis of 2',6'-dimethyltyrosine containing tritiated delta opioid-receptor selective antagonist dipeptide ligands with extraordinary affinity
AUTHOR(S): Kertesz, I.; Balboni, G.; Salvadori, S.; Lazarus, L. H.; Toth, G.
CORPORATE SOURCE: Institute of Biochemistry, Biological Research Centre of the Hungarian Academy of Sciences, Szeged, H-6701, Hung.
SOURCE: Journal of Labelled Compounds & Radiopharmaceuticals (**1998**), 41(12), 1083-1091
CODEN: JLCRD4; ISSN: 0362-4803
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A new class of δ-opioid antagonists was recently discovered in which the sequence Tyr-Tic was used as a message domain. The substitution of Tyr1 by Dmt (Dmt = 2',6'-dimethyltyrosine) enhanced the δ selectivity and antagonist activity. The excellent activity of these ligands was the reason for synthesizing the corresponding tritiated derivs. Peptides containing Tic (Tic = 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid) at position 2 undergo spontaneous diketopiperazine formation in some solvents, with a reduction in opioid activity. To avoid this side-reaction, the N,N-di-Me analog [N,N(Me)2-Dmt-Tic-OH] was synthesized and it was found to be stable. Thus, diiodinated forms of H-Dmt-Tic-OH and N,N(Me)2-Dmt-Tic-OH were prepared to undergo the catalytic dehalotritiation step. Tritiated dipeptides of high specific radioactivity were obtained: 44.67 Ci/mmol for [3H]Dmt-Tic-OH and 59.88 Ci/mmol for [3H]N,N(Me)2-Dmt-Tic-OH.
IT **220045-95-4P 220045-96-5P**
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(synthesis of dipeptides containing tritiated dimethyltyrosines as δ-opioid receptor antagonists)
IT **172262-39-4 178951-49-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of dipeptides containing tritiated dimethyltyrosines as δ-opioid receptor antagonists)
IT **220045-90-9P 220045-93-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of dipeptides containing tritiated dimethyltyrosines as δ-opioid receptor antagonists)
IT **220045-92-1P 220045-94-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of dipeptides containing tritiated dimethyltyrosines as δ-opioid receptor antagonists)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 14 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:597921 HCAPLUS
DOCUMENT NUMBER: 129:339945
TITLE: Subtleties of structure-δ agonist vs. δ antagonist relationships of opioid dipeptide derivatives
AUTHOR(S): Schiller, P. W.; Weltrowska, G.; Bolewska-Pedyczak, E.; Nguyen, T. M-D.; Lemieux, C.; Chung, N. N.
CORPORATE SOURCE: Laboratory of Chemical Biology and Peptide Research,

Clinical Research Institute of Montreal, Montreal, QC, H2W 1R7, Can.
SOURCE: Peptides 1996, Proceedings of the European Peptide Symposium, 24th, Edinburgh, Sept. 8-13, 1996 (**1998**), Meeting Date 1996, 785-786. Editor(s): Ramage, Robert; Epton, Roger. Mayflower Scientific: Kingswinford, UK.
CODEN: 66RCA5
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Recently, the authors reported that the dipeptide derivative H-Tyr-Tic-NH-(Ch2)2-Ph represents a new prototype of a moderately potent δ-selective opioid agonist. In the present paper, the authors describe how subtle structural modifications of this parent structure led to a potent and selective δ agonist, δ antagonists and mixed μ agonist/δ antagonists. Compds. were synthesized by solution methods and their opioid activity profiles were determined in vitro in the guinea pig ileum and mouse vas deferens bioassays and the rat brain membrane receptor binding assays.
IT **215596-98-8 215597-26-5 215597-37-8**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(subtleties of structure-δ agonist vs. δ antagonist relationships of opioid dipeptide derivs.)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

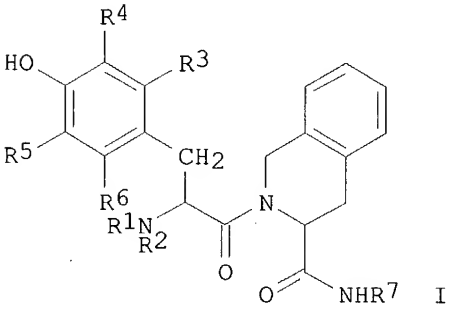
L15 ANSWER 15 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:507698 HCAPLUS
DOCUMENT NUMBER: 129:245476
TITLE: Conformationally constrained opioid peptide analogs with novel activity profiles
AUTHOR(S): Schiller, Peter W.; Schmidt, Ralf; Weltrowska, Grazyna; Berezowska, Irena; Nguyen, Thi M.-D.; Dupuis, Sebastien; Chung, Nga N.; Lemieux, Carole; Wilkes, Brian C.; Carpenter, Katharine A.
CORPORATE SOURCE: Laboratory of Chemical Biology and Peptide Research, Clinical Research Institute of Montreal, Montreal, QC, H2W 1R7, Can.
SOURCE: Letters in Peptide Science (**1998**), 5(2-3), 209-214
CODEN: LPSCEM; ISSN: 0929-5666
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Novel conformationally constrained opioid peptide analogs, having properties as δ antagonist, mixed μ agonist/δ antagonist or δ agonist, were developed. TIP(P)-related δ antagonists showed unprecedented δ antagonist potency and δ receptor selectivity, and may have potential for use in analgesia in combination with μ agonists. A definitive model of their δ receptor-bound conformation was developed. Three prototype mixed μ agonist/δ antagonists were discovered. They represent the only known compds. with this pharmacol. profile and, as expected, one of them was shown to be a potent analgesic and to produce no dependence and less tolerance than morphine. Novel dipeptide derivs. turned out to be potent and selective δ agonists. Because of their low mol. weight and lipophilic character, these compds. may cross the blood-brain barrier and, thus, may have potential as centrally acting analgesics.
IT **156219-37-3 160429-67-4 160429-68-5 172262-39-4 173927-99-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); BIOL (Biological study)
(activity profiles of conformationally constrained opioid peptide analogs)
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 16 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:479553 HCAPLUS
DOCUMENT NUMBER: 129:95725
TITLE: Preparation of dipeptide derivatives for treatment of pain
INVENTOR(S): Schiller, Peter
PATENT ASSIGNEE(S): Astra AB (Publ), Swed.
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE | |
|---|---|---|---|---|---|
| WO 9828327 | A1 | 19980702 | WO 1997-SE2156 | 19971218 | <-- |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | | |
| RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | | |
| AU 9855808 | A1 | 19980717 | AU 1998-55808 | 19971218 | <-- |
| AU 721131 | B2 | 20000622 | | | |
| EP 946588 | A1 | 19991006 | EP 1997-952145 | 19971218 | <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | | |
| NZ 336026 | A | 20010223 | NZ 1997-336026 | 19971218 | |
| JP 2001507026 | T2 | 20010529 | JP 1998-528696 | 19971218 | |
| US 6150335 | A | 20001121 | US 1998-43881 | 19980401 | |
| NO 9903069 | A | 19990621 | NO 1999-3069 | 19990621 | <-- |

PRIORITY APPLN. INFO.: SE 1996-4789 A 19961220
WO 1997-SE2156 W 19971218
OTHER SOURCE(S): MARPAT 129:95725
GI



I

AB Dipeptide derivs. I [R1, R2 = independently H, Me(CH2)n, Ph(CH2)m, cyclopropylmethyl, allyl; R3-R6 = H; R3 = C1-6 alkyl, R4-R6 = H; R3 = R6 = C1-6 alkyl, R4 = R5 = H; R3 = R5 = R6 = H, R4 = F, Cl, Br, iodo, OH, NO2,

NH2; R7 = (un)substituted 2-phenylethyl or 2-cyclohexylethyl; n = 0-12; m = 1-3] are claimed for the manufacture of a medicament for the treatment of pain. The compds. are δ opioid agonists and thus useful in the treatment of pain without the requirement of co-application of a μ opioid agonist. Thus, amidation of Boc-Tic-OH (Boc = Me3CO2C; Tic = L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid) with 2,2-diphenylethylamine, deprotection, peptide coupling with Boc-Tyr(Boc)-OH, and final deprotection gave desired dipeptide derivative H-Tyr-Tic-NHCH2CHPh2 (II). II and related dipeptide derivs. are selective δ opioid agonists, with II having Ki = 0.981 nM in a δ opioid receptor assay.

IT **209786-71-0P 209786-77-6P 209786-79-8P**
**209786-80-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of dipeptide derivs. for treatment of pain)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 17 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:102445 HCAPLUS
DOCUMENT NUMBER: 128:226374
TITLE: Rational design of dynorphin A analogs with δ-receptor selectivity and antagonism for δ- and κ-receptors
AUTHOR(S): Guerrini, Remo; Capasso, Anna; Marastoni, Mauro; Bryant, Sharon D.; Cooper, Peter S.; Lazarus, Lawrence H.; Temussi, Piero A.; Salvadori, Severo
CORPORATE SOURCE: Department of Pharmaceutical Sciences and Biotechnology Center, University of Ferrara, Ferrara, I-44100, Italy
SOURCE: Bioorganic & Medicinal Chemistry (**1998**), 6(1), 57-62
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Substitution of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) in place of Gly2 in dynorphin A-(1-13)-NH2 and -(1-11)-NH2 (DYN) analogs (1 and 2) decreased the affinity to the κ, δ, and μ receptors, and κ selectivity. The analog [D-Ala2, des-Gly3]DYN (4), a chimera between deltorphin/dermorphin N-terminal tripeptide and DYN, was virtually inactive for κ-sites while the affinities for δ- and μ-receptors remained essentially unchanged. The doubly substituted analog [2',6'-dimethyl-L-tyrosine (Dmt1)-Tic2]DYN (3) exhibited high δ-affinity (Ki=0.39 nM) while μ- and κ-affinities were only an order of magnitude less (4-5 nM). Bioactivity of [Tic2]DYN peptides (1-3) on guinea-pig ileum and rabbit jejunum revealed potent δ- and κ-antagonism, while the δ agonist potency of 4 was comparable to DYN. Thus, conversion from a κ-agonist to antagonist occurred with the inclusion of Tic into DYN analogs, similar to the appearance of antagonist properties with δ- and μ-opioid agonists containing a Tic2 residue.

IT **204764-01-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(rational design of dynorphin A analogs with δ-receptor selectivity and antagonism for δ- and κ-receptors)

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 18 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:20189 HCAPLUS
DOCUMENT NUMBER: 128:162532
TITLE: The stereochemical requirements of the novel δ-opioid selective dipeptide antagonist TMT-TIC
AUTHOR(S): Liao, Subo; Lin, Jun; Shenderovich, Mark D.; Han, Yinglin; Hasohata, Keiko; Davis, Peg; Qiu, Wei; Porreca, Frank; Yamamura, Henry I.; Hruby, Victor J.
CORPORATE SOURCE: Department of Chemistry, The University of Arizona, Tucson, AZ, 85721, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (**1997**), 7(23), 3049-3052
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Five conformationally constrained dipeptide TMT-L-Tic analogs have been synthesized and evaluated for their bioactivity using in vitro bioassays. The most potent and selective analog (2S,3R)-TMT-L-Tic showed 9 nM binding affinity and 4000-fold selectivity for the δ vs. μ opioid receptor. The lowest-energy conformation of (2S,3R)-TMT-L-Tic is suggested to be bioactive one in which the χ1 torsional angle is trans for TMT and gauche (+) for Tic.
IT **202860-53-5P 202860-54-6P 202860-55-7P**
**202860-56-8P 202860-57-9P**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(stereochem. requirements of the novel δ-opioid selective dipeptide antagonist TMT-TIC)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 19 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:594750 HCAPLUS
DOCUMENT NUMBER: 127:248425
TITLE: Isoquinolines useful as analgesics
INVENTOR(S): Dimaio, John; Wang, Wuyi
PATENT ASSIGNEE(S): Astra AB, Swed.; Dimaio, John; Wang, Wuyi
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE | |
|---|---|---|---|---|---|
| WO 9731940 | A1 | 19970904 | WO 1997-SE315 | 19970225 | <-- |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | | |
| CA 2244219 | AA | 19970904 | CA 1997-2244219 | 19970225 | <-- |
| AU 9721090 | A1 | 19970916 | AU 1997-21090 | 19970225 | <-- |
| AU 722032 | B2 | 20000720 | | | |
| CN 1211990 | A | 19990324 | CN 1997-192558 | 19970225 | <-- |
| EP 914332 | A1 | 19990512 | EP 1997-906381 | 19970225 | <-- |
| EP 914332 | B1 | 20020508 | | | |

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

| | | | | | |
|---|---|---|---|---|---|
| BR 9707767 | A | 19990727 | BR 1997-7767 | 19970225 | <-- |
| JP 2000506138 | T2 | 20000523 | JP 1997-530865 | 19970225 | |
| NZ 331119 | A | 20000526 | NZ 1997-331119 | 19970225 | |
| AT 217322 | E | 20020515 | AT 1997-906381 | 19970225 | |
| US 6034097 | A | 20000307 | US 1997-930867 | 19971006 | <-- |
| NO 9803945 | A | 19981006 | NO 1998-3945 | 19980827 | <-- |

PRIORITY APPLN. INFO.: SE 1996-769 A 19960228
WO 1997-SE315 W 19970225

OTHER SOURCE(S): MARPAT 127:248425

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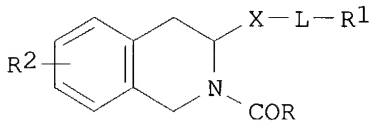

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AB Peptidomimetic isoquinolines I [X = CH2NHCO, CH2NHCO2, CONH, CH2NH; L = (un)substituted alkyl; R = 3-aryl- or 3-aralkyl-2-pyrrolidinyl or -2-piperidinyl, 1-[(un)substituted amino]alkyl or -aralkyl; R1 = aryl, aralkyl, alkyl; R2 = alkyl, H, OH, halo, SH, NO2, NH2, alkylamino, NH:C(NH2), NH:C(NH2)NH, CO2H or carbalkoxy] were prepared as analgesics. Thus, 2-[2-guanidino-3-(4-hydroxy-2,6-dimethylphenyl)propionyl]-1,2,3,4-tetrahydroisoquinoline-3-S-carboxylic acid (2-R-hydroxy-3-phenylpropyl)amide bistrifluoroacetate was prepared and assayed for analgesic activity (Kiμ = 2.03±0.37, Kiδ = 0.56±0.09, and Kiκ = 276.6±13.6 nM).

IT **195831-57-3P 195831-71-1P 195831-73-3P**
**195831-77-7P 195831-82-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(isoquinolines useful as analgesics)

IT **195832-13-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(isoquinolines useful as analgesics)

IT **195831-53-9P 195831-55-1P 195831-59-5P**
**195831-61-9P 195831-63-1P 195831-65-3P**
**195831-67-5P 195831-69-7P 195831-75-5P**
**195831-78-8P 195831-80-2P 195831-84-6P**
**195831-86-8P 195831-88-0P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(isoquinolines useful as analgesics)

L15 ANSWER 20 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:565015 HCAPLUS
DOCUMENT NUMBER: 127:214595
TITLE: Evolution of the Dmt-Tic Pharmacophore: N-Terminal Methylated Derivatives with Extraordinary δ Opioid Antagonist Activity
AUTHOR(S): Salvadori, Severo; Balboni, Gianfranco; Guerrini, Remo; Tomatis, Roberto; Bianchi, Clementina; Bryant, Sharon D.; Cooper, Peter S.; Lazarus, Lawrence H.
CORPORATE SOURCE: Department of Pharmaceutical Science and Biotechnology Center, University of Ferrara, Ferrara, 44100, Italy
SOURCE: Journal of Medicinal Chemistry (**1997**),

40(19), 3100-3108
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The δ opioid antagonist H-Dmt-Tic-OH (2',6'-dimethyl-L-tyrosyl-1,2,3,4-tetrahydro-3-isoquinoline-3-carboxylic acid) exhibits extraordinary δ receptor binding characteristics [Kiδ = 0.022 nM; Kiμ/Kiδ = 150 000] and δ antagonism (pA2 = 8.2; Ke = 5.7 nM). A change in chirality of Dmt at Cα curtailed δ receptor parameters, while replacement of its α-amino function by a Me group led to inactivity; Tyr-Tic analogs weakly interacted with δ receptors. N-Alkylation of H-Dmt-Tic-OH and H-Dmt-Tic-Ala-OH with Me groups produced potent δ opioid ligands with high δ receptor binding capabilities and enhanced δ antagonism: (i) N-Me-Dmt-Tic-OH had high δ opioid binding (Kiδ = 0.2 nM), elevated δ antagonism on mouse vas deferens (MVD) (pA2 = 8.5; Ke = 2.8 nM), and nondetectable μ activity with guinea pig ileum (GPI). (Ii) N,N-Me2-Dmt-Tic-OH was equally efficacious in δ receptor binding (Kiδ = 0.12 nM; Kiμ/Kiδ = 20 000), but δ antagonism rose considerably (pA2 = 9.4; Ke = 0.28 nM) with weak μ antagonism (pA2 = 5.8; Ke = 1.58 μM; GPI/MVD = 1:5640). N-Me- and N,N-Me2-Dmt-Tic-Ala-OH also augmented δ opioid receptor binding, such that N,N-Me2-Dmt-Tic-Ala-OH demonstrated high affinity (Kiδ = 0.0755 nM) and selectivity (Kiμ/Kiδ = 20 132) with exceptional antagonist activity on MVD (pA2 = 9.6; Ke = 0.22 nM) and weak antagonism on GPI (pA2 = 5.8; Ke = 1.58 μM; GPI/MVD = 1:7180). Although the amidated dimethylated dipeptide analog had high Kiδ (0.31 nM) and excellent antagonist activity (pA2 = 9.9; Ke = 0.12 nM), the increased activity toward μ receptors in the absence of a free acid function at the C-terminus revealed a modest δ selectivity (Kiμ/Kiδ = 1 655) and somewhat comparable bioactivity (GPI/MVD = 4500). Thus, the data demonstrate that N,N-(Me)2-Dmt-Tic-OH and N,N-Me2-Dmt-Tic-Ala-OH retained high δ receptor affinities and δ selectivities and acquired enhanced potency in pharmacol. bioassays on MVD greater than that of other peptide or non-peptide δ antagonists.

IT **189094-51-7P 194857-52-8P 194857-55-1P**
**194857-60-8P 194857-61-9P 194857-62-0P**
**194857-64-2P 194857-66-4P 194857-69-7P**
**194857-71-1P 194857-72-2P 194857-74-4P**
**194857-76-6P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(preparation of dimethyltyrosyl isoquinolinecarboxylate derivs. as δ opioid antagonists)

IT **172262-39-4 172262-40-7 172262-47-4**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(preparation of dimethyltyrosyl isoquinolinecarboxylate derivs. as δ opioid antagonists)

IT **189093-95-6P 194857-79-9P 194857-81-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of dimethyltyrosyl isoquinolinecarboxylate derivs. as δ opioid antagonists)

L15 ANSWER 21 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:455179 HCAPLUS
DOCUMENT NUMBER: 127:171672
TITLE: Design and solution structure of a partially rigid

opioid antagonist lacking the basic center. Models of antagonism

AUTHOR(S): Crescenzi, Orlando; Fraternali, Franca; Picone, Delia; Tancredi, Teodorico; Balboni, Gianfranco; Guerrini, Remo; Lazarus, Lawrence H.; Salvadori, Severo; Temussi, Piero A.

CORPORATE SOURCE: Dipartimento di Chimica, Universita di Napoli Federico II, Naples, I-80134, Italy

SOURCE: European Journal of Biochemistry (**1997**), 247(1), 66-73
CODEN: EJBCAI; ISSN: 0014-2956

PUBLISHER: Springer

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To discriminate between two general models of antagonism (participation and allosteric), an opioid antagonist lacking the basic nitrogen of tyramine was designed and characterized. Cyclo-[Tyr(Me)2-Tic-], the diketopiperazine of 2,6-dimethyltyrosyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, is a partially rigid opioid antagonist; its pA2 (5.8) is one smaller than that of N,N-bisallyl-enkephalin but it has a very high binding affinity (10 nM) and has a δ selectivity (66 with respect to the binding to μ receptors) higher than that of naltrindole. The conformational state of this diketopiperazine, studied under a variety of solvent and temperature conditions by NMR and mol. dynamics, can be described in terms of only three conformers whose relative populations vary widely with solvent. Only one of the three conformers, characterized by a 90° arrangement of the aromatic rings of Tyr(Me)2 and Tic similar to those of rigid agonists and of the bioactive conformation of the corresponding linear antagonist, is consistent with the antagonist activity. This finding favors the participation model among the general mechanisms proposed to explain antagonism. Due to the simple composition of the conformational mixture and to the rigidity of the mol., it is possible to propose a quant. explanation for the discrepancy between the very high binding affinity (10 nM) and the fairly small in mouse vas deferens value (1.5 μM).

IT **178951-47-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(structure of a partially rigid opioid antagonist lacking the basic center)

IT **193897-93-7**
RL: RCT (Reactant); RACT (Reactant or reagent)
(structure of a partially rigid opioid antagonist lacking the basic center)

IT **172262-40-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(structure of a partially rigid opioid antagonist lacking the basic center design and solution)

L15 ANSWER 22 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:101287 HCAPLUS

DOCUMENT NUMBER: 126:288045

TITLE: Opioid diketopiperazines. Synthesis and activity of a prototypic class of opioid antagonists

AUTHOR(S): Balboni, Gianfranco; Guerrini, Remo; Salvadori, Severo; Tomatis, Roberto; Bryant, Sharon D.; Bianchi, Clementina; Attila, Martti; Lazarus, Lawrence H.

CORPORATE SOURCE: Biotechnology Center, Univ. Ferrara, Ferrara, I-44100, Italy

SOURCE: Biological Chemistry (**1997**), 378(1), 19-29
CODEN: BICHF3; ISSN: 1431-6730

PUBLISHER: de Gruyter

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Discovery of high affinity and ultraselective δ opioid dipeptide antagonists composed of 2',6'-dimethyl-L-tyrosine (Dmt) and 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) served as the basis for the conformationally restricted diketopiperazine cyclo(Dmt-Tic) and related open chain analogs. These peptides primarily bind to δ-opioid receptors: c(Dmt-Tic) displayed 30- to 50-fold higher δ affinity (Kiδ) than its diastereomeric analogs and more than 4000-fold greater than its Tyr cognate; all of the c(Tyr-Tic) analogs were essentially inactive; c[(N-methyl)Dmt-Tic] lost 5-fold in Kiδ, while KiM, increased 10-fold to yield a nonselective peptide; and the c(Dmt-Phe) series exhibited considerably reduced binding which indicated a synergism between Dmt and Tic in the binding mechanism. Whereas acetyl-Dmt-Tic linear peptides weakly interacted with opioid receptors, Ac-Dmt-Tic-NH2, exhibited better δ antagonist activity than c(Dmt-Tic) and greater δ receptor selectivity (Kiμ/Kiδ = 570). A 3 point attachment hypothesis for the interaction between c(Dmt-Tic) and the δ receptor was proposed: hydrophobicity imparted by the aromatic rings and the Me groups of Dmt, H bonding through the tyramine OH group, and cation-π interactions were suggested as contributing factors in binding the diketopiperazine in the receptor pocket. Although c(Dmt-Tic) exhibited a weak antagonist activity with mouse vas deferens, this diketopiperazine may provide a scaffolding for the formation of more potent antagonists for potential therapeutic applications.
IT **178951-45-6P 178951-46-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation and activity of prototypic diketopiperazine δ-opioid antagonists)
IT **178951-47-8P 178951-48-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and activity of prototypic diketopiperazine δ-opioid antagonists)
IT **189094-01-7**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation and activity of prototypic diketopiperazine δ-opioid antagonists)
IT **189093-93-4P 189093-95-6P 189094-05-1P 189094-07-3P 189094-51-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and activity of prototypic diketopiperazine δ-opioid antagonists)

L15 ANSWER 23 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:714329 HCAPLUS
DOCUMENT NUMBER: 126:26958
TITLE: Development of potent opioid δ antagonists and mixed μ agonist/δ antagonists
AUTHOR(S): Schiller, P. W.; Schmidt, R.; Wilkes, B. C.; Weltrowska, G.; Nguyen, T. M. -D.; Chung, N. N.; Lemieux, C.
CORPORATE SOURCE: Laboratory Chemical Biology and Peptide Research, Clinical Research Institute Montreal, Montreal, QC, H2W 1R7, Can.
SOURCE: Peptides: Biology and Chemistry, Proceedings of the Chinese Peptide Symposium, 3rd, Beijing, June 13-17,

1994 (**1995**), Meeting Date 1994, 140-143.
Editor(s): Lu, Gui-Shen; Tam, James P.; Du, Yu-Cang.
ESCOM: Leiden, Neth.
CODEN: 63QWA5
DOCUMENT TYPE: Conference
LANGUAGE: English
AB An analog of TIPP (Tyr-Tic-Phe-Phe) is reported which is a mixed μ agonist/δ antagonist with both greatly enhanced μ agonist potency and still very high δ antagonist activity.
IT **160429-67-4 161669-02-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(potent opioid δ antagonists and mixed μ agonist/δ antagonists)

L15 ANSWER 24 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:639557 HCAPLUS
DOCUMENT NUMBER: 126:1296
TITLE: Novel opioid peptide analogs with mixed μ agonist/δ antagonist properties
AUTHOR(S): Schiller, P. W.; Weltrowska, G.; Nguyen, T. M. -D.; Lemieux, C.; Chung, N. N.
CORPORATE SOURCE: Clinical Research Institute Montreal, Montreal, QC, H2W 1R7, Can.
SOURCE: Peptides 1994, Proceedings of the European Peptide Symposium, 23rd, Braga, Port., Sept. 4-10, 1994 (**1995**), Meeting Date 1994, 632-633. Editor(s): Maia, Hernani L. S. ESCOM: Leiden, Neth.
CODEN: 63MBAO
DOCUMENT TYPE: Conference
LANGUAGE: English
AB In an effort to strengthen the agonist component of TIPP-NH2, the authors substituted 2',6'-dimethyltyrosine (Dmt) for Tyr1. The resulting compound, H-Dmt-Tic-Phe-Phe-NH2 (DIPP-NH2), displayed a potent agonist effect in the GPI assay. This effect was reversed by a low dose of naloxone (Ke = 2.42 nmol dm-3), indicating that it was mediated by receptors. In the MVD assay DIPP-NH2 was a potent antagonist with a value in the subnanomolar range. In comparison with the parent compound TIPP-NH2, DIPP-NH2 showed 65 times higher receptor affinity and 25 times higher affinity in the opioid receptor binding assays. Reduction of the peptide bond between Tic and Phe in DIPP-NH2 resulted in a pseudopeptide analog, H-Tyr-Tic[CH2-NH]Phe-Phe-NH2, which was an agonist with twice the potency of DIPP-NH2 in the GPI assay and again showed a low Ke value (1.25 nmol dm-3) for naloxone as antagonist.
IT **160429-67-4 160429-68-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(novel opioid peptide analogs with mixed μ agonist/δ antagonist properties)

L15 ANSWER 25 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:462678 HCAPLUS
DOCUMENT NUMBER: 125:158369
TITLE: Dmt-TIC-OH, a highly selective and potent δ-opioid dipeptide receptor antagonist after systemic administration in the mouse
AUTHOR(S): Capasso, Anna; Guerrini, Remo; Balboni, Gianfranco; Sorrentino, Ludovico; Temussi, Pierandrea; Lazarus, Lawrence H.; Bryant, Sharon D.; Salvadori, Severo
CORPORATE SOURCE: Sch. Pharmacy, Univ. Salerno, Italy
SOURCE: Life Sciences (**1996**), 59(8), PL 93-PL 98
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Dmt-Tic-OH (DTOH) and Dmt-Tic-Ala-OH (DTAOH), effective antagonists, in vitro, represent new potent opioid dipeptides for the δ-opioid receptor (Kiδ of 0.022 nM and a selectivity, Kiμ/Kiδ, of 150,000 for DTOH; Kiδ of 0.285 nM and a selectivity Kiμ/Kiδ, of 20,4 for DTAOH). In the present study we considered the pharmacol. activity of these two new δ opioid peptide receptor antagonists in vivo. Therefore, we have evaluated their possible antagonistic activity against the antinociception induced by the highly selective δ opioid receptor agonist, [D-Ala2]deltorphin II (DEL). Furthermore, these two δ opioid peptide receptor antagonists were injected centrally or peripherally in order to assess their ability to act also after systemic administration. Concurrent i.c.v. injection of DTOH or DTAOH (0.5-1.0-2.0 nM) with DEL (5 nmol) induced a significant reduction of DEL antinociception. By contrast, while DTOH (10-20-40 mg/kg) administered peripherally (i.p., s.c. or i.v.) was also able to reduce DEL antinociception, DTAOH failed. The present results indicate that DTOH is the first opioid dipeptide with δ antagonist activity after systemic administration and it could be important in clin. and therapeutic applications.
IT **172262-39-4 172262-47-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. activity of δ opioid receptor antagonists Dmt-Tic-OH and Dmt-Tic-Ala-OH)

L15 ANSWER 26 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:447008 HCAPLUS
DOCUMENT NUMBER: 125:105145
TITLE: Ultraselective δ-opioid mimetic peptides containing dimethyltyrosine and tetrahydroisoquinoline carboxylate and pharmacological and therapeutic uses thereof
INVENTOR(S): Lazarus, Lawrence H.; Salvadori, Severo; Temussi, Piero Andrea
PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE | |
|---|---|---|---|---|---|
| WO 9616982 | A2 | 19960606 | WO 1995-US15510 | 19951130 | <-- |
| WO 9616982 | A3 | 19961024 | | | |
| W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK | | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | | |
| US 5780589 | A | 19980714 | US 1994-347531 | 19941130 | <-- |
| AU 9644639 | A1 | 19960619 | AU 1996-44639 | 19951130 | <-- |

PRIORITY APPLN. INFO.: US 1994-347531 19941130
WO 1995-US15510 19951130
OTHER SOURCE(S): MARPAT 125:105145
AB Novel opioid mimetic dipeptides, tripeptides and cyclic peptides exhibit enhanced affinity and selectivity for δ-opioid receptors. The

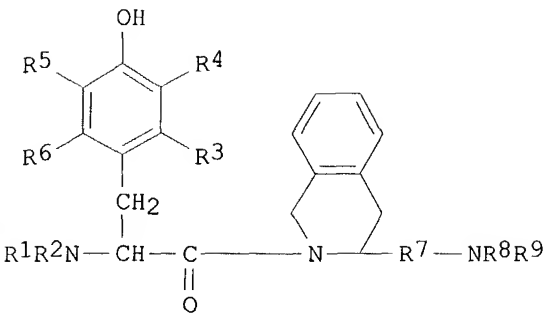
peptides are represented by the formulas L/D-Dmt-L-/D-Tic-R', L/D-R"-Dmt-L/D-Tic-R'; L/D-Dmt-L-/D-Tic-R-R'; L/D-R"-Dmt-L/D-Tic-R-R'; and cyclic (L/D-Dmt-L/D-Tic) wherein Dmt is 2',6'-dimethyl-L/D-tyrosine, Tic is L/D-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, R is a natural or unusual aliphatic amino residue, R' is a functional group at the carboxyl terminus of the peptide and R" is a functional group at the amino terminus of the peptide. Pharmacol. and therapeutic compns. are also provided.

IT **172262-39-4 172262-40-7 172262-41-8**
**172262-42-9 172262-47-4 172262-48-5**
**172339-67-2 172339-68-3 178951-42-3**
**178951-45-6 178951-46-7 178951-47-8**
**178951-48-9 178951-49-0 178951-50-3**
**178951-51-4 178951-52-5 179091-74-8**
**179091-75-9**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(δ-opioid mimetic; ultraselective δ-opioid mimetic peptides containing dimethyltyrosine and tetrahydroisoquinoline carboxylate and pharmacol. and therapeutic uses thereof)

L15 ANSWER 27 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:431375 HCAPLUS
DOCUMENT NUMBER: 125:87219
TITLE: Preparation of new peptide derivatives with delta opioid receptor antagonist or mixed mu agonist/delta antagonist effects
INVENTOR(S): Schiller, Peter
PATENT ASSIGNEE(S): Astra Aktiebolag, Swed.
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE | |
|---|---|---|---|---|---|
| WO 9606855 | A1 | 19960307 | WO 1995-SE918 | 19950810 | <-- |
| W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM | | | | | |
| RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | | |
| ZA 9506561 | A | 19960229 | ZA 1995-6561 | 19950804 | <-- |
| CA 2197566 | AA | 19960307 | CA 1995-2197566 | 19950810 | <-- |
| AU 9534016 | A1 | 19960322 | AU 1995-34016 | 19950810 | <-- |
| AU 695175 | B2 | 19980806 | | | |
| EP 776332 | A1 | 19970604 | EP 1995-930752 | 19950810 | <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | | |
| JP 10504837 | T2 | 19980512 | JP 1995-508658 | 19950810 | <-- |
| US 5811400 | A | 19980922 | US 1995-532688 | 19951006 | <-- |
| FI 9700823 | A | 19970227 | FI 1997-823 | 19970227 | <-- |
| NO 9700889 | A | 19970227 | NO 1997-889 | 19970227 | <-- |

PRIORITY APPLN. INFO.: SE 1994-2880 19940830
WO 1995-SE918 19950810
OTHER SOURCE(S): MARPAT 125:87219
GI



I

AB Compds. of formula [I; R1 = H, Me(CH2)n (wherein n = 0-12), CH2CH2Ph, cyclopropylmethyl, allyl, H-Arg; R2 = H, Me(CH2)n (wherein n = 0-12), cyclopropylmethyl, allyl; R3 - R6 = H; or R4 = R5 = H and R3, R6 = C1-6 alkyl; R3 = R5 = R6 = H and R4 = F, Cl, Br, OH, or NO2; R7 = CO, CH2; R8 = H, C1-12 alkyl, aryl-C1-12 alkyl; R9 = linear or branched C1-12 alkyl, aryl-C1-2 alkyl, C1-12 alkyl-linked to a heterocyclic moiety], which show high potency as δ antagonists or a mixed μ agonist/δ antagonist properties with total lack of μ antagonist properties, have a low mol. weight and are highly lipophilic, facilitate passage across the brain blood-barrier, and are useful in therapy, especially as analgesics and as immunosuppressive agents, are prepared Thus, Boc-Tic-OH (Tic = 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid residue) was treated with iso-Bu chloroformate in THF at -15° for 3-4 min, coupled with H2N(CH2)3Ph at -15° for 30 min, and stirred with CF3CO2H containing 3% thioanisole under ice-cooling to give 95% H-Tic-NH(CH2)3Ph.CF3CO2H. The latter compound was similarly coupled with Boc-Tyr(Boc)-OH in the presence of N-methylmorpholine and deprotected with CF3CO2H to give, after HPLC purification, 80% H-Tyr-Tic-NH(CH2)3Ph. All compds. showed δ-antagonist properties and no μ antagonist activity in the guinea pig ileum assay at concns. as high as 10 μM and were either partial or full μ agonists in the guinea pig ileum assay. In particular, H-Dmt-Tic-NHCH2CH2Q (Q = CH2Ph, cyclohexyl, 3-indolyl; Dmt = 2',6'-dimethyltyrosine) were potent mixed μ agonist/δ antagonists.

IT **178752-43-7P 178752-50-6P 178752-53-9P 178752-57-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of new peptide derivs. with δ opioid receptor antagonist or mixed μ agonist/δ antagonist effects as analgesics and immunosuppressants)

L15 ANSWER 28 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:196729 HCAPLUS
DOCUMENT NUMBER: 124:261755
TITLE: Preparation of opioid peptide analogs as δ opioid receptor antagonists
INVENTOR(S): Schiller, Peter
PATENT ASSIGNEE(S): Astra Aktiebolag, Swed.
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| WO 9535316 | A1 | 19951228 | WO 1995-SE721 | 19950614 <-- |
| W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT | | | | |
| RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| ZA 9504311 | A | 19960122 | ZA 1995-4311 | 19950526 <-- |
| CA 2192484 | AA | 19951228 | CA 1995-2192484 | 19950614 <-- |
| AU 9528114 | A1 | 19960115 | AU 1995-28114 | 19950614 <-- |
| AU 691630 | B2 | 19980521 | | |
| EP 777682 | A1 | 19970611 | EP 1995-923629 | 19950614 <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| JP 10501807 | T2 | 19980217 | JP 1995-502047 | 19950614 <-- |
| US 5733881 | A | 19980331 | US 1995-507370 | 19950822 <-- |
| NO 9605457 | A | 19961218 | NO 1996-5457 | 19961218 <-- |
| FI 9605116 | A | 19961219 | FI 1996-5116 | 19961219 <-- |

PRIORITY APPLN. INFO.: SE 1994-2170 19940620
SE 1994-2838 19940825
WO 1995-SE721 19950614

OTHER SOURCE(S): MARPAT 124:261755
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title peptides [I; R1 = H, Me(CH2)n, PhCH2CH2, cyclopropylmethyl, CH2:CHCH2, H-Arg; wherein n = 0-12; R2 = H, Me (CH2)n, cyclopropylmethyl, CH2:CHCH2; wherein n = 0-12; R3 - R6 = H; R4 = R5 = H and R3 = R6 = C1-6 alkyl; R3 = R5 = R6 = H and R4 = F, Cl, Br, OH, NH2, or NO2; R7 = CO, CH2; R8 = H, C1-6 alkyl; R9 = bivalent radical selected from Me(CH2)mCH, Me2CHCH, Me2CHCH2CH, EtCHMeCH, HOCH2CH, MeSCH2CH2CH, Q; wherein p = 0-4; R10 = OH, NH2, Q1, Q2; R11 = H, NO2, F, Cl, Br, iodo; q = 0-3; R12 = CO2H, CONH2, CH2OH, any addnl. amino acid or peptide segment], which are useful in therapy, especially as analgesics and as immunosuppressive agents, are prepared Thus, 3.48 g BOP was added to a stirred solution of 2.8 g Boc-Tic-OH (N-tert-butoxycarbonyl-L-1,2,3,4-tetrahydroquinoline) and 1.33 mL Et3N in CH2Cl2. After 5 min, 1.2 g N-dimethylhydroxylamine hydrochloride and 1.68 mL Et3N were added and the reaction was carried out for 17 h to give, after silica gel chromatog., 65% N-tert-butoxycarbonyl-L-1,2,3,4-tetrahydroquinoline-3-N-methoxy-N-methylcarboxamide, which (1.2 g) was reduced by 190 mg LiAlH4 in Et2O for 1 h to give the aldehyde N-tert-butoxycarbonyl-L-1,2,3,4-tetrahydroquinoline-3-carboxaldehyde (Boc-Tic-H). The resin H-Cha-Phe-O-resin (Cha = cyclohexylalanine) (preparation given) was washed twice with DMF , successively treated with Boc-Tic-H in DMF containing 1% AcOH and then portion wise with 115 mg NaBH3CN. After coupling the N-terminal tyrosine and deprotection, the peptide was cleaved from the resin, purified, and lyophilized to give H-Tyr-TicΠ[CH2-NH]Cha-Phe-OH.

IT **174860-13-0P 174860-14-1P 174860-15-2P**
**174860-17-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of opioid peptide analogs as δ opioid receptor antagonists, analgesics, and immunosuppressants)

L15 ANSWER 29 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:17570 HCAPLUS

DOCUMENT NUMBER: 124:164281
TITLE: Four different types of opioid peptides with mixed μ agonist/δ antagonist properties
AUTHOR(S): Schiller, P. W.; Weltrowska, G.; Schmidt, R.; Nguyen, T. M. -D.; Berezowska, I.; Lemieux, C.; Chung, N. N.; Carpenter, K. A.; Wilkes, B. C.
CORPORATE SOURCE: Laboratory Chemical Biology and Peptide Research, Clinical Research Institute Montreal, Montreal, QC, H2W 1R7, Can.
SOURCE: Analgesia (Elmsford, New York) (**1995**), 1(4-6), 703-6
CODEN: AALGEB; ISSN: 1071-569X
PUBLISHER: Cognizant Communication Corp.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mixed μ agonist/δ antagonists are thought to have potential as analgesics with low propensity to produce tolerance and dependence. The first balanced μ agonist/δ antagonist was the pseudotetrapeptide H-Dmt-Ticψ[CH2-NH]Phe-Phe-NH2 (DIPP-NH2[ψ]; Dmt = 2',6'-dimethyltyrosine; Tic = tetrahydroisoquinoline-3-carboxylic acid), which showed very high μ agonist potency in the GPI assay, excellent δ antagonist potency in the MVD assay and μ and δ receptor affinities in the subnanomolar range. The dipeptide derivative H-Dmt-Tic-NH-(CH2)3-Ph (Ph = phenyl) displayed similarly high μ and δ receptor affinities and appears to be a mixed partial μ agonist/δ antagonist. Another class of mixed μ agonist/δ antagonists are cyclic β-casomorphin analogs containing a 2-naphthylalanine (2-Nal) residue in the 3-position of the peptide sequence, the prototype being H-Tyr-c[-D-Orn-2-Nal-D-Pro-Gly-]. An analog of this type, H-Dmt-c[-D-Orn-2-Nal-D-Pro-Gly-], also showed balanced μ agonist/δ antagonist potencies in the subnanomolar range. The novel cyclic opioid peptide H-c(Lys-Dmt-D-Ala-Phe-Asp)-H2 turned out to be yet another prototype of a mixed μ agonist/δ antagonist.

IT **160429-68-5 173927-99-6**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(mixed μ agonist/δ antagonist opioids as analgesics with low tolerance and dependence)

L15 ANSWER 30 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:7265 HCAPLUS
DOCUMENT NUMBER: 124:75581
TITLE: Conformational analysis of potent and very selective δ opioid dipeptide antagonists
AUTHOR(S): Amodeo, P.; Balboni, G.; Crescenzi, O.; Guerrini, R.; Picone, D.; Salvadori, S.; Tancredi, T.; Temussi, P. A.
CORPORATE SOURCE: ICMIB del CNR, via Toiano 6, 80072 Arco Felice, Naples, Italy
SOURCE: FEBS Letters (**1995**), 377(3), 363-7
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The δ selectivity and antagonism of peptides containing L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) in second position can be attributed mainly to the Tyr-Tic unit. These properties can be further enhanced by substituting Tyr1 with 2,6-dimethyl-L-tyrosyl (Dmt). Dmt-Tic-NH2, Dmt-Tic-OH, Dmt-Tic-Ala-NH2 and Dmt-Tic-Ala-OH are all more active and/ or selective than the corresponding [Tyr1]-parent peptides. In fact, the selectivities of Dmt-Tic-OH and Dmt-Tic-Ala-OH are the highest ever recorded for opioid mols. The 1H NMR spectra in a

DMSO/water mixture at 278 K reveal the presence of two similar conformers, characterized by a cis or trans Dmt-Tic bond, in all four peptides. A detailed conformational anal. in solution of Dmt-Tic-NH2 shows that these conformers have a shape very similar to that of the bioactive conformation of Tyr-Tic-NH2 and to that of naltrindole.

IT **172262-39-4 172262-40-7 172262-47-4**
**172262-48-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(conformational anal. of potent and selective δ-opioid dipeptide antagonists)

L15 ANSWER 31 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:944609 HCAPLUS
DOCUMENT NUMBER: 124:75511
TITLE: δ Opioidmimetic antagonists: prototypes for designing a new generation of ultraselective opioid peptides
AUTHOR(S): Salvadori, Severo; Attila, Martti; Balboni, Giofranco; Bianchi, Clementina; Bryant, Sharon D.; Crescenzi, Orlando; Guerrini, Remo; Picone, Delia; Tancredi, Teodorico; et al.
CORPORATE SOURCE: Department of Pharmaceutical Sciences, University of Ferrara, Ferrara, Italy
SOURCE: Molecular Medicine (Cambridge, Massachusetts) (**1995**), 1(6), 678-89
CODEN: MOMEF3; ISSN: 1076-1551
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tyr-Tic (1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid) and Tyr-Tic-Ala were the first peptides with δ opioid antagonist activity lacking Phe, considered essential for opioid activity based on the N-terminal tripeptide sequence (Tyr-D-Xaa-Phe) of amphibian skin opioids. Analogs were then designed to restrain the rotational flexibility of Tyr by the substitution of 2,6-dimethyl-L-tyrosine (Dmt). Tyr and Dmt peptides were synthesized by solid phase and solution methods using Fmoc technol. or condensing Boc-Dmt-OH or Boc-Tyr(But)-OH with H-L-Tic-OBut or H-D-Tic-OBut, resp. Peptides were purified (>99%) by HPLC and characteristics determined by 1H-NMR, FAB-MS, m.p., TLC, and amino acid analyses. H-Dmt-Tic-OH had high affinity (Kiδ = 0.022 nM) and extraordinary selectivity (Kiμ/Kiδ = 150,000); H-Dmt-Tic-Ala-OH had a Kiδ = 0.29 nM and δ selectivity = 20,000. Affinity and selectivity increased 8700- and 1000-fold relative to H-Tyr-Tic-OH, resp. H-Dmt-Tic-OH and H-Dmt-Tic-NH2 fitted one-site receptor binding models (η = 0.939-0.987), while H-Dmt-Tic-ol, H-Dmt-Tic-Ala-OH and H-Dmt-Tic-Ala-NH2 best fitted two-site models (η = 0.708-0.801, F 18.9-26.0, $p < 0.0001$). Amidation increased μ affinity by 10- to 100-fold and acted synergistically with D-Tic2 to reverse selectivity (δ → μ). Dmt-Tic di- and tripeptides exhibited δ antagonist bioactivity (Ke = 4-66 nM) with mouse vas deferens and lacked agonist μ activity (> 10 μM) in guinea-pig ileum prepns. Dmt-Tic analogs weakly interacted with κ receptors in the 1 to >20 μM range. Dmt-Tic opioidmimetic peptides represent a highly potent class of opioid peptide antagonists with greater potency than the nonopioid δ antagonist naltrindole and have potential application as clin. and therapeutic compds.

IT **172262-39-4P 172262-40-7P 172262-41-8P**
**172262-42-9P 172262-43-0P 172262-47-4P**
**172262-48-5P 172339-67-2P 172339-68-3P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study);

PREP (Preparation); PROC (Process); USES (Uses)
(δ opioidmimetic antagonists: prototypes for designing a new generation of ultraselective opioid peptides)

L15 ANSWER 32 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:428717 HCAPLUS
DOCUMENT NUMBER: 122:188168
TITLE: Preparation of peptides as δ opioid antagonists.
INVENTOR(S): Schiller, Peter
PATENT ASSIGNEE(S): Aktiebolaget Astra, Swed.
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

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| AU 9458448 | A1 | 19940815 | AU 1994-58448 | 19931220 | <-- |
| AU 681372 | B2 | 19970828 | | | |
| EP 678099 | A1 | 19951025 | EP 1994-904365 | 19931220 | <-- |
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| JP 08505386 | T2 | 19960611 | JP 1993-515914 | 19931220 | <-- |
| US 5602099 | A | 19970211 | US 1994-176938 | 19940104 | <-- |
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| CN 1096515 | A | 19941221 | CN 1994-100129 | 19940105 | <-- |
| LV 10962 | B | 19970420 | LV 1995-197 | 19950629 | <-- |
| FI 9503302 | A | 19950704 | FI 1995-3302 | 19950704 | <-- |
| NO 9502650 | A | 19950830 | NO 1995-2650 | 19950704 | <-- |

PRIORITY APPLN. INFO.: SE 1993-12 19930105
WO 1993-SE1090 19931220

OTHER SOURCE(S): MARPAT 122:188168
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. [I; R1 = H, Me(CH2)n, PhCH2CH2, cyclopropylmethyl, allyl, H-Arg; R2 = H, Me(CH2)n, cyclopropylmethyl, allyl, etc.; n = 0-12; R3-R6 = H, or R4, R5 both = H and R3, R6 both = lower alkyl, or R3, R5, R6all = H and R4 = F, Cl, Br, OH, NH2, NO2; R7 = CO, CH2; R8= H, lower alkyl; R9= Q1-Q7; m = 0-2; R10 = H, F, Cl, Br, iodo; R11 = OH, NH2, Q8, Q9; R12 = H, NO2, F, Cl, Br, iodo; m = 0-2; R13, R14 = CO2H, CONH2, CH2OH, amino acid or peptide segment; with the exceptions of compds. where R1, R2, R3, R4, R5, R6, R8 all = H, R7 = CO, R9 = PhCH2CH, and R11 = Phe-OH, Phe-NH2, OH, NH2], were prepared Thus, H-Tyr-Tic-Hfe-Phe-OH (Tic = 1,2,3,4-tetrahydroisoquinoline-3-carboxylate; Hfe = homophenylalanyl), was prepared by solid phase synthesis. I antagonized [Leu5] enkephalin in mouse vas deferens with Ke = 0.169-43.9 nM.

IT **156219-37-3 160429-67-4 160429-68-5**
**161669-02-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptides as δ opioid antagonists)

L15 ANSWER 33 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:259490 HCAPLUS
DOCUMENT NUMBER: 122:71781
TITLE: A highly potent TIPP-NH2 analog with balanced mixed μ agonist/δ antagonist properties
AUTHOR(S): Schiller, P. W.; Weltrowska, G.; Nguyen, T. M.-D.; Lemieux, C.; Chung, N. N.; Wilkes, B. C.
CORPORATE SOURCE: Lab. Chem. Biol. Peptide Res., Clin. Res. Inst. Montreal, Montreal, QC, H2W 1R7, Can.
SOURCE: Regulatory Peptides (**1994**), 54(1), 257-8
CODEN: REPPDY; ISSN: 0167-0115
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The tetrapeptide amide H-Tyr-Tic-Phe-Phe-NH2 (TIPP-NH2; Tic = tetrahydroisoquinoline-3-carboxylic acid) has recently been shown to be a moderately potent μ opioid agonist and a highly potent δ opioid antagonist, thus representing the first known example of a mixed μ agonist/δ antagonist. In an effort to strengthen the μ agonist component of TIPP-NH2, the authors substituted 2',6'-dimethyltyrosine (Dmt) for Tyr1. The analogs H-Dmt-Tic-Phe-Phe-NH2 (DIPP-NH2) and H-Dmt-TicΨ[CH2-NH]Phe-Phe-NH2 (DIPP-NH2[Ψ]) were both potent μ agonists in the GPI assay (IC50 = 13.5 nM and 7.71 nM, resp.) and potent antagonists against δ agonists in the MVD assay (Ke .apprx. 0.2 nM and 0.5 nM, resp.). In the rat brain membrane binding assays, DIPP-NH2 and DIPP-NH2[Ψ] showed very high μ receptor affinities (Kiμ = 1.19 nM and 0.94 nM, resp.) and δ receptor affinities (Kiδ = 0.12 nM and 0.45 nM, resp.). DIPP-NH2[Ψ] represents the first known opioid compound with balanced mixed μ agonist/δ antagonist properties.
IT **160429-67-4 160429-68-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(highly potent tetrapeptide amide analog with balanced mixed μ opioid agonist/δ opioid antagonist properties)

L15 ANSWER 34 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:450365 HCAPLUS
DOCUMENT NUMBER: 121:50365
TITLE: TIPP analogs: highly selective δ opioid antagonists with subnanomolar potency and first known compounds with mixed μ agonists/δ antagonist properties
AUTHOR(S): Schiller, P. W.; Weltrowska, G.; Nguyen, T. M. D.; Chung, N.; Lemieux, C.; Wilkes, B. C.
CORPORATE SOURCE: Lab. Chem. Biol. Peptides Res., Clin. Res. Inst. Montreal, Montreal, QC, H2W 1R7, Can.
SOURCE: Regulatory Peptides (**1994**), (Suppl. 1), S63-S64
CODEN: REPPDY; ISSN: 0167-0115
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Analogs of the potent and highly selective δ-opioid antagonist H-Tyr-Tic-Phe-Phe-OH (TIPP) (Tic = tetrahydroisoquinoline-3-carboxylic acid) containing Trp, 3-(2'-naphthyl)alanine (2-Nal), or homophenylalanine (Hfe) in place of Phe3, or p-nitrophenylalanine [Phe(pNO2)] in place of Phe4 exhibited a 1.5-5-fold increase in δ antagonist potency against δ agonists in the mouse vas deferens (MVD) assay and 3-5-fold enhanced δ selectivity. The pseudopeptide H-Tyr-TicΨ[CH2-NH]Phe-

Phe-OH (TIPP[Ψ]) showed excellent stability against enzymic degradation, high δ antagonist potency (Ke .apprx.2.5 nM), no μ antagonist properties, and unprecedented δ selectivity, being 500 times more selective than the nonpeptide δ antagonist naltrindole. The analog H-Dmt-Tic-Phe-Phe-OH (DIPP) (Dmt = 2,6-dimethyltyrosine) displayed a Ke of 0.15 nM and is the most potent δ antagonist reported to date. Both H-Tyr-Tic-Phe-Phe-NH2 and DIPP were moderately potent, full μ agonists in the guinea pig ileum assay and thus represent the first mixed μ agonist/δ antagonists known.

IT **156219-37-3**
RL: BIOL (Biological study)
(as μ agonist/δ antagonist)

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E1 THROUGH E164 ASSIGNED

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DICTIONARY FILE UPDATES:  17 JUN 2004  HIGHEST RN 694921-36-3

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161       RN   161669-02-9  REGISTRY
162       RN   160429-68-5  REGISTRY
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164       RN   156219-37-3  REGISTRY


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L16  ANSWER 1 OF 164  REGISTRY  COPYRIGHT 2004 ACS on STN
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     (9CI)  (CA INDEX NAME)
FS   STEREOSEARCH
MF   C30 H35 N3 O3
SR   CA
LC   STN Files:   CA, CAPLUS
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RL.NP  Roles from non-patents:  BIOL (Biological study); PREP (Preparation);
       USES (Uses)

Absolute stereochemistry.
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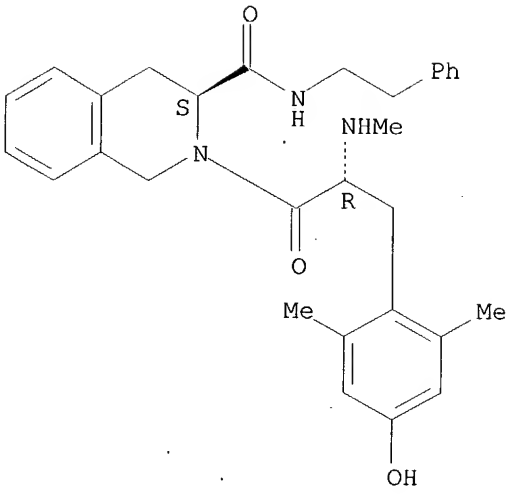


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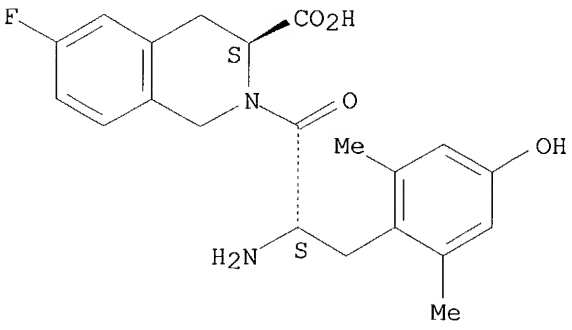
REFERENCE 1: 135:40848

L16 ANSWER 5 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **329320-07-2** REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-6-fluoro-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C21 H23 F N2 O4
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PROC (Process)

Absolute stereochemistry.

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REFERENCE 1: 134:216792

L16 ANSWER 13 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **329319-99-5** REGISTRY
CN 7-Isoquinolinamine, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)
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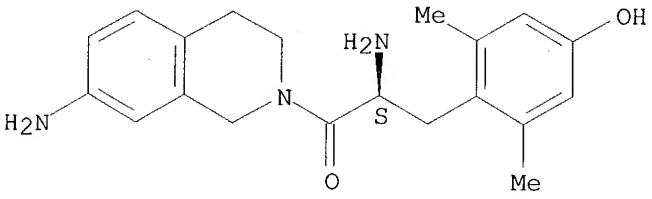
MF C20 H25 N3 O2
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process)

Absolute stereochemistry.



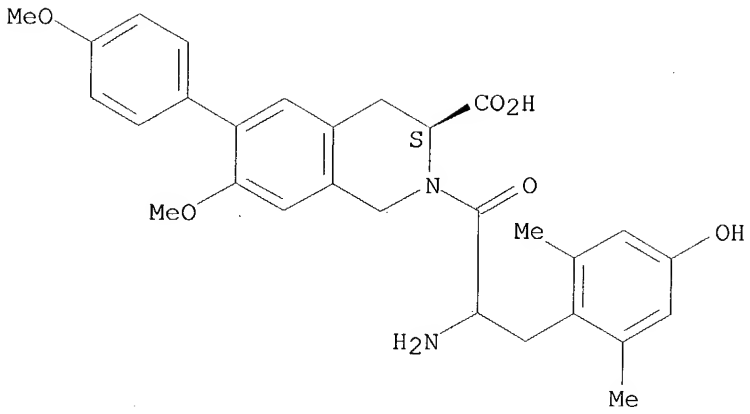

**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 134:216792

L16 ANSWER 17 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **262616-51-3** REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-7-methoxy-6-(4-methoxyphenyl)-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C29 H32 N2 O6
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process)

Absolute stereochemistry.



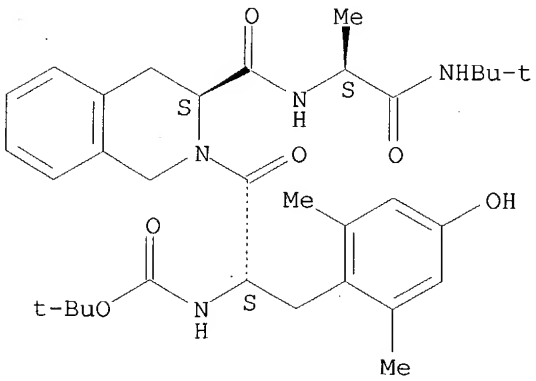

**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 132:245845

L16 ANSWER 35 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **254102-28-8** REGISTRY
CN Carbamic acid, [(1S)-2-[(3S)-3-[[[(1S)-2-[(1,1-dimethylethyl)amino]-1-methyl-2-oxoethyl]amino]carbonyl]-3,4-dihydro-2(1H)-isoquinolinyl]-1-[(4-hydroxy-2,6-dimethylphenyl)methyl]-2-oxoethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C33 H46 N4 O6
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: PREP (Preparation); RACT (Reactant or reagent)
RL.NP Roles from non-patents: PREP (Preparation); RACT (Reactant or reagent)

Absolute stereochemistry. Rotation (+).




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:338140

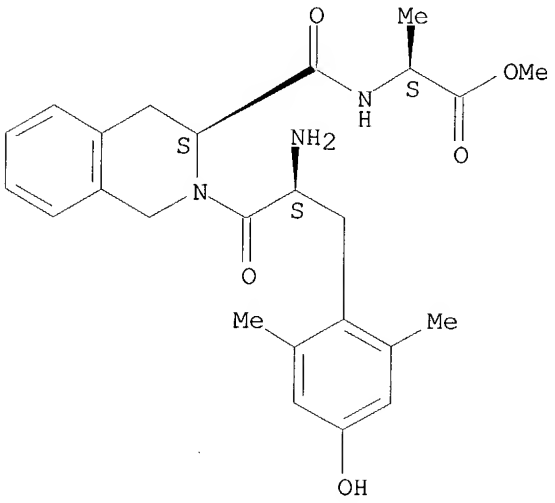
REFERENCE 2: 132:73213

L16 ANSWER 51 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **254101-98-9** REGISTRY
CN L-Alanine, N-[[(3S)-2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinyl]carbonyl]-, methyl ester, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C25 H31 N3 O5 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation)

CM 1

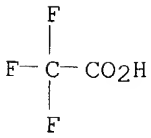
CRN 254101-97-8
CMF C25 H31 N3 O5

Absolute stereochemistry. Rotation (+).




CM 2

CRN 76-05-1
CMF C2 H F3 O2



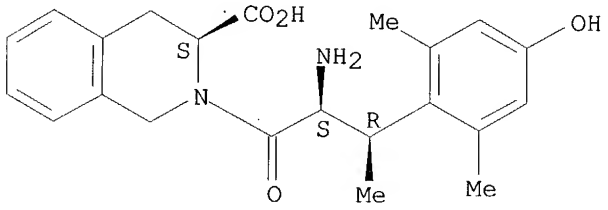

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:338140

REFERENCE 2: 132:73213

L16 ANSWER 65 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **250331-76-1** REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[(2S,3R)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxobutyl]-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN TMT-Tic
FS STEREOSEARCH
MF C22 H26 N2 O4
CI COM
SR CA
LC STN Files: BIOSIS, CA, CAPLUS
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study)
RL.NP Roles from non-patents: BIOL (Biological study)

Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:143750

REFERENCE 2: 139:111815

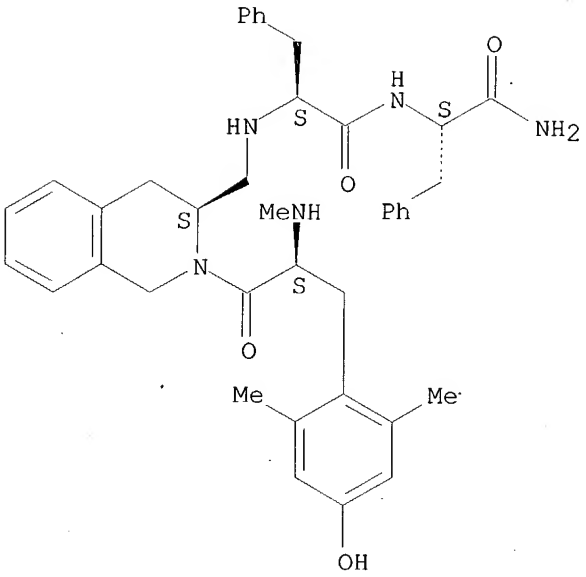
REFERENCE 3: 138:248480

REFERENCE 4: 131:347049

L16 ANSWER 66 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **245538-29-8** REGISTRY
CN L-Phenylalaninamide, N-[[(3S)-1,2,3,4-tetrahydro-2-[(2S)-3-(4-hydroxy-2,6-dimethylphenyl)-2-(methylamino)-1-oxopropyl]-3-isoquinolinyl]methyl]-L-phenylalanyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C40 H47 N5 O4
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

Absolute stereochemistry.

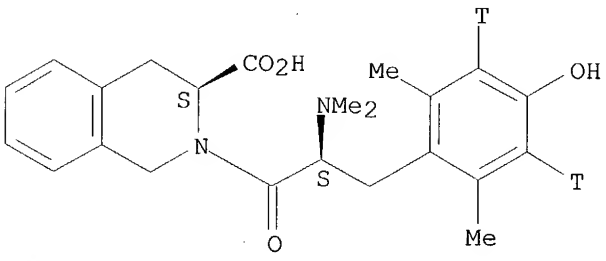


1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 131:266894

L16 ANSWER 68 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **220045-96-5** REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[(2S)-2-(dimethylamino)-3-(4-hydroxy-2,6-dimethylphenyl-3,5-t2)-1-oxopropyl]-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C23 H26 N2 O4 T2
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Conference; Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties)

Absolute stereochemistry.



3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

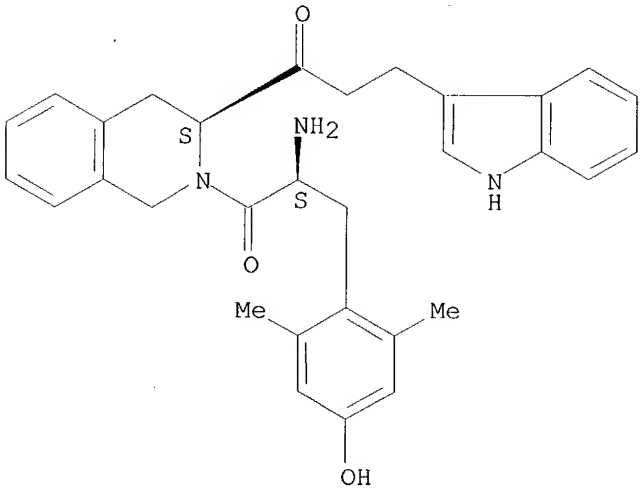
REFERENCE 1: 133:99680

REFERENCE 2: 131:214535

REFERENCE 3: 130:139633

L16 ANSWER 74 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **215597-37-8** REGISTRY
CN Isoquinoline, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-3-[3-(1H-indol-3-yl)-1-oxopropyl]-, (3S)-(9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H33 N3 O3
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Conference
RL.NP Roles from non-patents: BIOL (Biological study); PROC (Process); PRP (Properties)

Absolute stereochemistry.



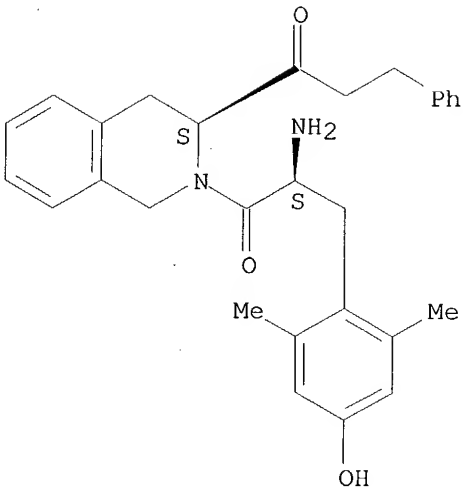

**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 129:339945

L16 ANSWER 76 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **215596-98-8** REGISTRY
CN Isoquinoline, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-3-(1-oxo-3-phenylpropyl)-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C29 H32 N2 O3
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Conference
RL.NP Roles from non-patents: BIOL (Biological study); PROC (Process); PRP (Properties)

Absolute stereochemistry.



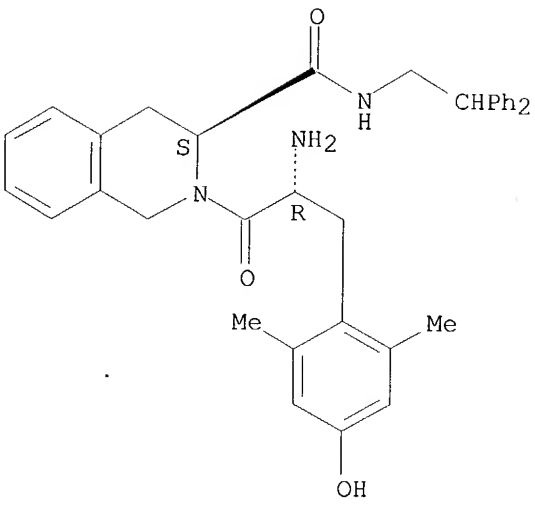

**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 129:339945

L16 ANSWER 77 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **209786-80-1** REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2R)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-N-(2,2-diphenylethyl)-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C35 H37 N3 O3
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

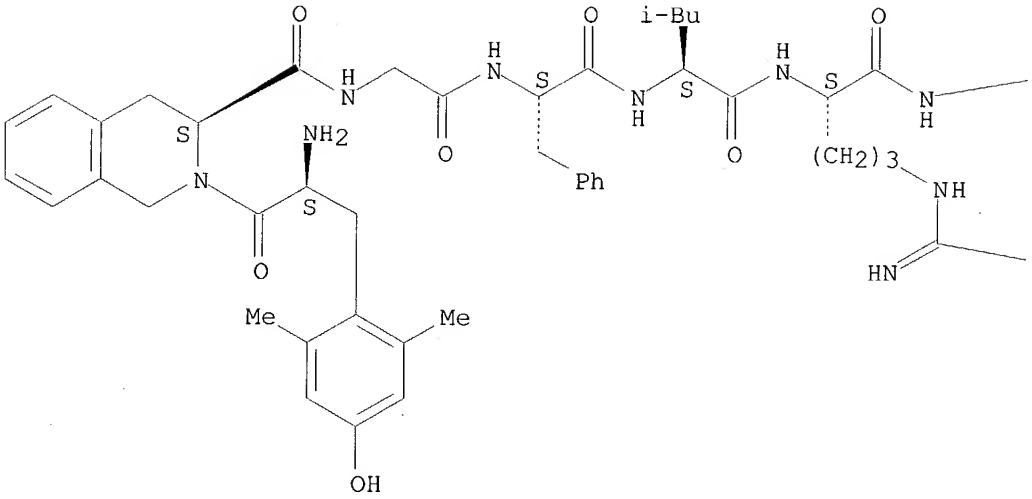
REFERENCE 1: 129:95725

L16 ANSWER 81 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **204764-01-2** REGISTRY
CN 1-11-Dynorphin A (swine), 1-(N,O-dimethyl-L-tyrosine)-2-[(3S)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid]-11-L-lysinamide- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C73 H114 N22 O12
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PRP (Properties)

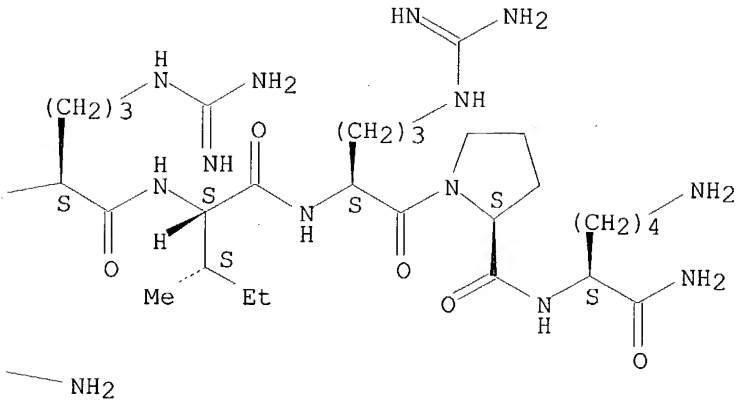
**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

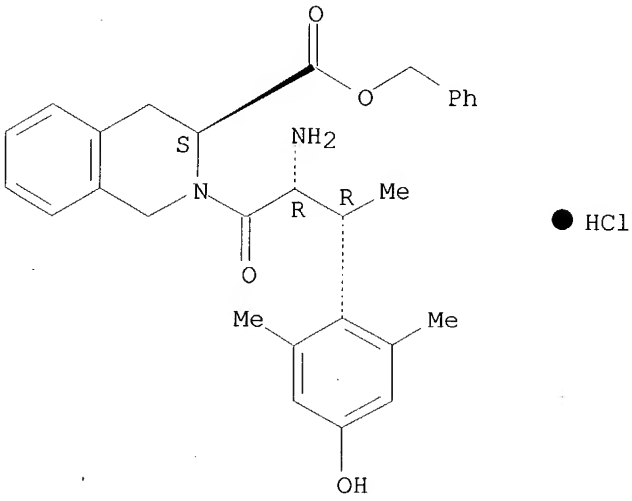
REFERENCE 1: 128:226374

=>
=>
=> d ide can l16 82 87 88 107 125 126 130 132 134 143 147 151 152 154 161 162 164

L16 ANSWER 82 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **202860-57-9** REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxobutyl]-1,2,3,4-tetrahydro-, phenylmethyl ester, monohydrochloride, [3S-[2(2S*,3S*),3R*]]- (9CI) (CA INDEX NAME)

FS STEREOSEARCH
MF C29 H32 N2 O4 . Cl H
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties)

Absolute stereochemistry.

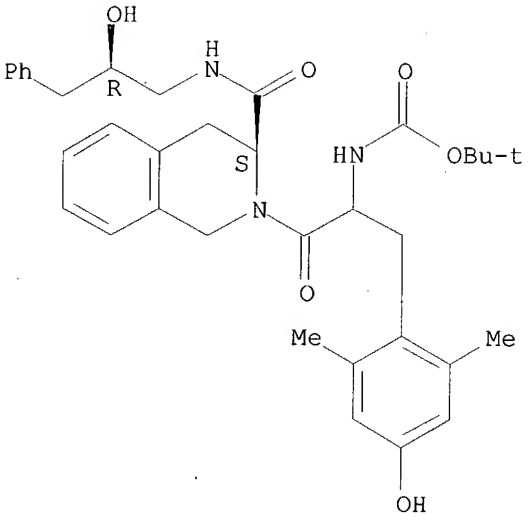



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 128:162532

L16 ANSWER 87 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **195832-13-4** REGISTRY
CN Carbamic acid, [2-[3,4-dihydro-3-[[(2-hydroxy-3-phenylpropyl)amino]carbonyl]-2(1H)-isoquinolinyl]-1-[(4-hydroxy-2,6-dimethylphenyl)methyl]-2-oxoethyl]-, 1,1-dimethylethyl ester, [3S-[3R*(S*)]]-[partial]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C35 H43 N3 O6
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: PREP (Preparation); RACT (Reactant or reagent)

Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

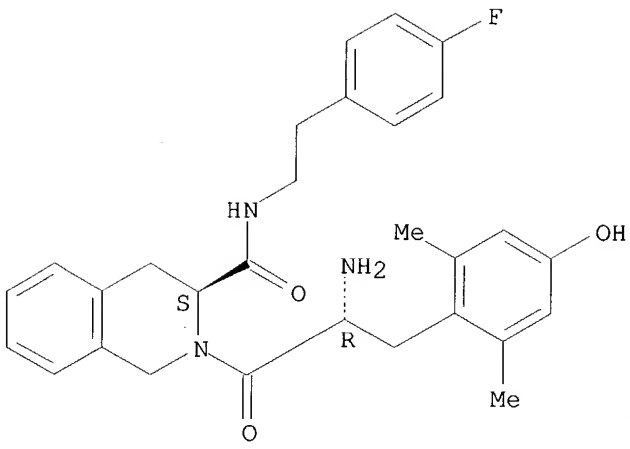
REFERENCE 1: 127:248425

L16 ANSWER 88 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **195831-88-0** REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-N-[2-(4-fluorophenyl)ethyl]-1,2,3,4-tetrahydro-, [S-(R*,S*)]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C29 H32 F N3 O3 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

CM 1

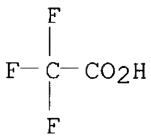
CRN 195831-87-9
CMF C29 H32 F N3 O3

Absolute stereochemistry.




CM 2

CRN 76-05-1
CMF C2 H F3 O2




1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

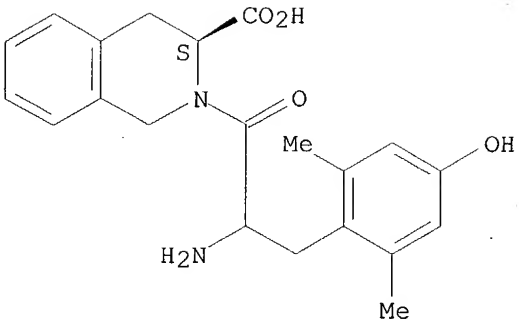
REFERENCE 1: 127:248425

L16 ANSWER 107 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **194857-81-3** REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C21 H24 N2 O4 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: PREP (Preparation); RACT (Reactant or reagent)

CM 1

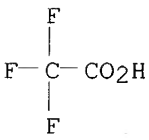
CRN 194857-80-2
CMF C21 H24 N2 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

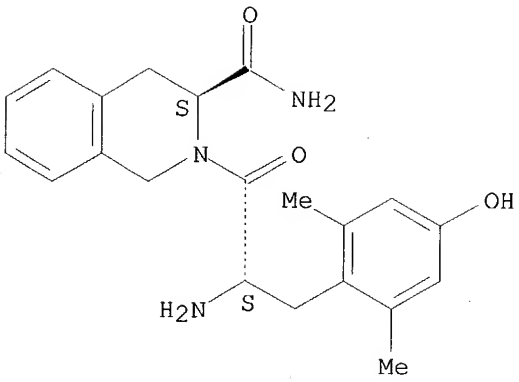
REFERENCE 1: 127:214595

L16 ANSWER 125 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **193897-93-7** REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-, [S-(R*,R*)]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C21 H25 N3 O3 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: RACT (Reactant or reagent)

CM 1

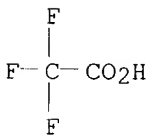
CRN 172262-40-7
CMF C21 H25 N3 O3

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

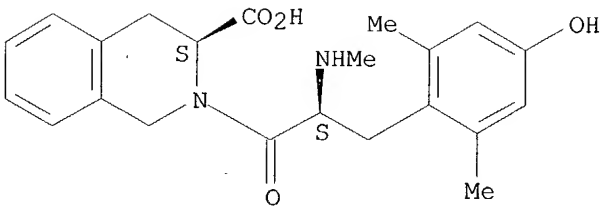
REFERENCE 1: 127:171672

L16 ANSWER 126 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **189094-51-7** REGISTRY
CN 3-Isoquinolinecarboxylic acid, 1,2,3,4-tetrahydro-2-[3-(4-hydroxy-2,6-dimethylphenyl)-2-(methylamino)-1-oxopropyl]-, [S-(R*,R*)]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H26 N2 O4 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)

CM 1

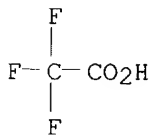
CRN 178951-51-4
CMF C22 H26 N2 O4

Absolute stereochemistry. Rotation (+).



CM 2

CRN 76-05-1
CMF C2 H F3 O2



2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 127:214595

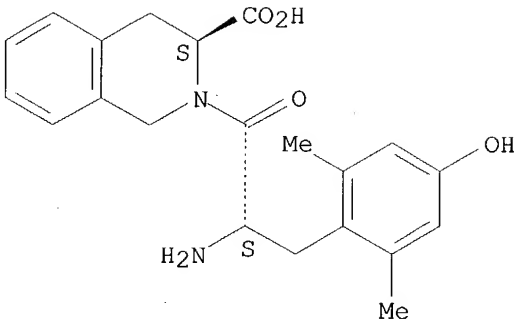
REFERENCE 2: 126:288045

L16 ANSWER 130 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **189093-95-6** REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C21 H24 N2 O4 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: RACT (Reactant or reagent)
RL.NP Roles from non-patents: PREP (Preparation); RACT (Reactant or reagent)

CM 1

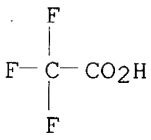
CRN 172262-39-4
CMF C21 H24 N2 O4

Absolute stereochemistry. Rotation (+).



CM 2

CRN 76-05-1
CMF C2 H F3 O2



4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:338140

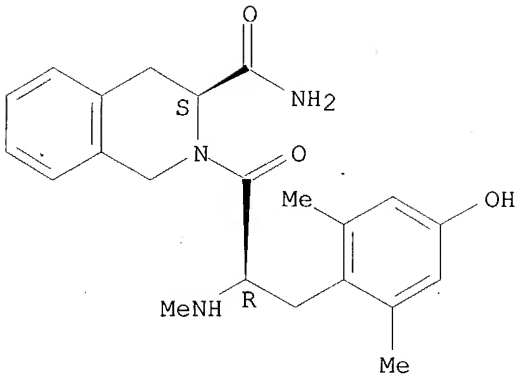
REFERENCE 2: 132:73213

REFERENCE 3: 127:214595

REFERENCE 4: 126:288045

L16 ANSWER 132 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **179091-75-9** REGISTRY
CN 3-Isoquinolinecarboxamide, 1,2,3,4-tetrahydro-2-[3-(4-hydroxy-2,6-dimethylphenyl)-2-(methylamino)-1-oxopropyl]-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H27 N3 O3
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PROC (Process); PRP (Properties); USES (Uses)

Absolute stereochemistry. Rotation (+).



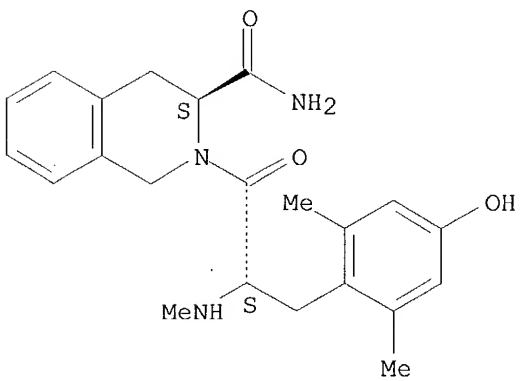
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 125:105145

L16 ANSWER 134 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **178951-52-5** REGISTRY
CN 3-Isoquinolinecarboxamide, 1,2,3,4-tetrahydro-2-[(2S)-3-(4-hydroxy-2,6-dimethylphenyl)-2-(methylamino)-1-oxopropyl]-, (3S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Isoquinolinecarboxamide, 1,2,3,4-tetrahydro-2-[3-(4-hydroxy-2,6-dimethylphenyl)-2-(methylamino)-1-oxopropyl]-, [S-(R*,R*)]-
FS STEREOSEARCH
MF C22 H27 N3 O3
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Conference; Patent
RL.P Roles from patents: BIOL (Biological study); PROC (Process); PRP (Properties); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study)

Absolute stereochemistry. Rotation (+).



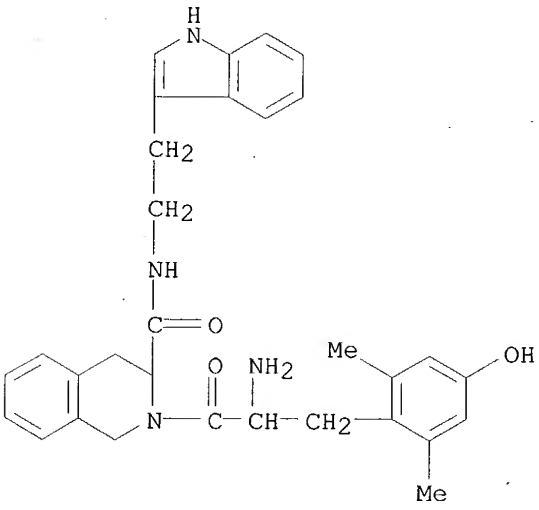
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 131:200061

REFERENCE 2: 125:105145

L16 ANSWER 143 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **178752-57-3** REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-[2-(1H-indol-3-yl)ethyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C31 H34 N4 O3
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

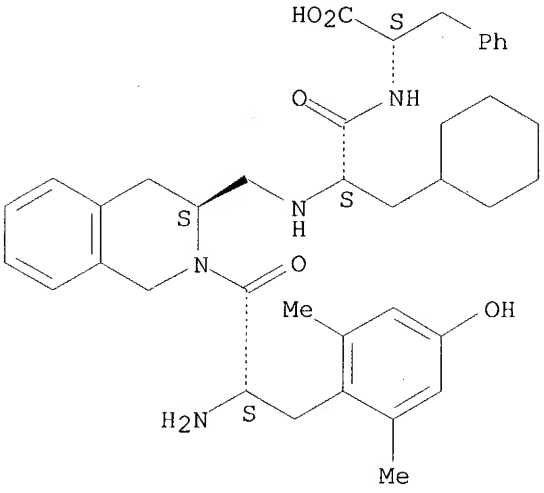
REFERENCE 1: 125:87219

L16 ANSWER 147 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **174860-17-4** REGISTRY
CN L-Phenylalanine, N-[[2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl]-3-cyclohexyl-L-alanyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C39 H50 N4 O5
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

Absolute stereochemistry.

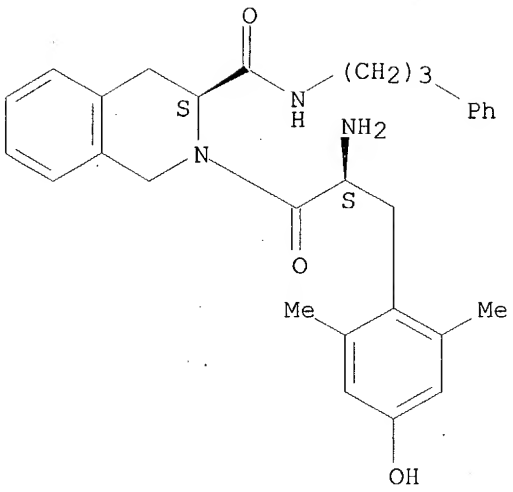



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 124:261755

L16 ANSWER 151 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **173927-99-6** REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-(3-phenylpropyl)-, (3S)-(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Isoquinolinecarboxamide, 2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-(3-phenylpropyl)-, [S-(R*,R*)]-
FS STEREOSEARCH
MF C30 H35 N3 O3
CI COM
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Conference; Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

Absolute stereochemistry.



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

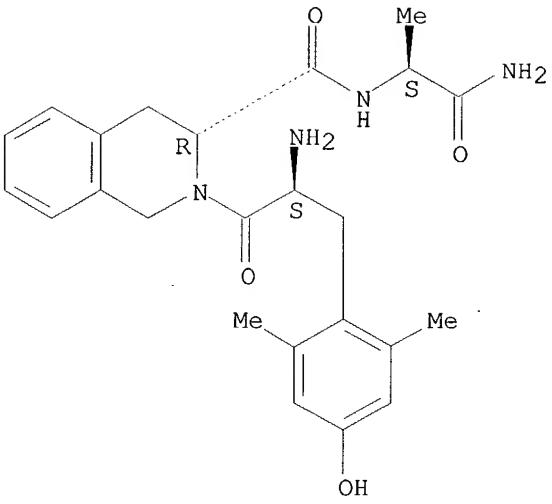
REFERENCE 1: 135:40848

REFERENCE 2: 129:245476

REFERENCE 3: 124:164281

L16 ANSWER 152 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **172339-68-3** REGISTRY
CN L-Alaninamide, 2,6-dimethyl-L-tyrosyl-D-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H30 N4 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PROC (Process); PRP (Properties); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

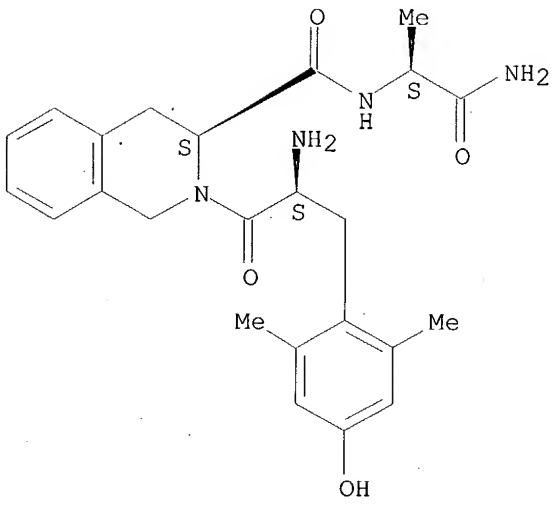
2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 125:105145

REFERENCE 2: 124:75511

L16 ANSWER 154 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **172262-48-5** REGISTRY
CN L-Alaninamide, 2,6-dimethyl-L-tyrosyl-(3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Alaninamide, 2,6-dimethyl-L-tyrosyl-L-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-
OTHER NAMES:
CN DTA (peptide)
FS STEREOSEARCH
MF C24 H30 N4 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PROC (Process); PRP (Properties); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

Absolute stereochemistry.



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

7 REFERENCES IN FILE CA (1907 TO DATE)
7 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:338140

REFERENCE 2: 135:235885

REFERENCE 3: 134:66089

REFERENCE 4: 132:73213

REFERENCE 5: 125:105145

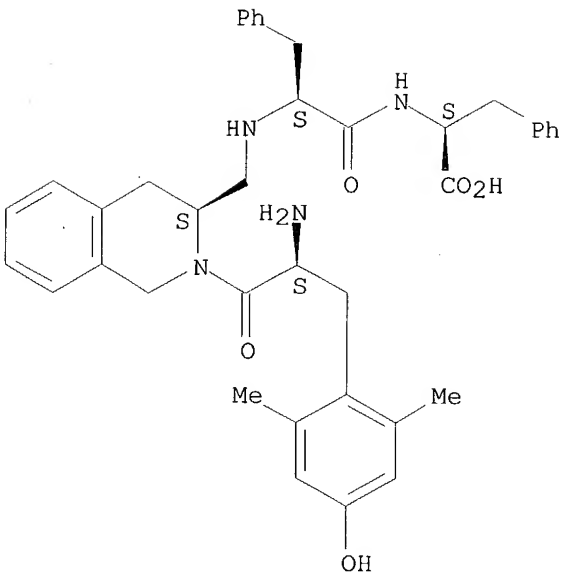
REFERENCE 6: 124:75581

REFERENCE 7: 124:75511

L16 ANSWER 161 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **161669-02-9** REGISTRY
CN L-Phenylalanine, N-[[(3S)-2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl]-L-phenylalanyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Phenylalanine, N-[N-[[2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl]-L-phenylalanyl]-, [S-(R*,R*)]-
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C39 H44 N4 O5
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Conference; Patent
RL.P Roles from patents: BIOL (Biological study); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); PRP (Properties)

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

Absolute stereochemistry.



2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

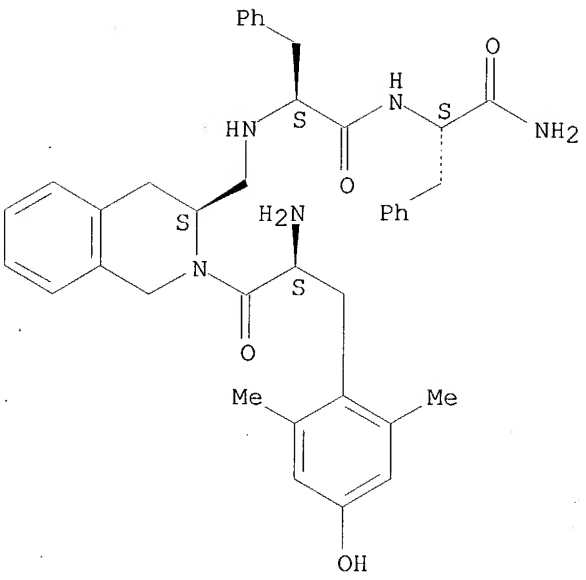
REFERENCE 1: 126:26958

REFERENCE 2: 122:188168

L16 ANSWER 162 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **160429-68-5** REGISTRY
CN L-Phenylalaninamide, N-[[(3S)-2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl]-L-phenylalanyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Phenylalaninamide, N-[[2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl]-L-phenylalanyl-, [S-(R*,R*)]-
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C39 H45 N5 O4
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Conference; Journal; Patent
RL.P Roles from patents: BIOL (Biological study); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

Absolute stereochemistry.



6 REFERENCES IN FILE CA (1907 TO DATE)
6 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 131:266894

REFERENCE 2: 129:245476

REFERENCE 3: 126:1296

REFERENCE 4: 124:164281

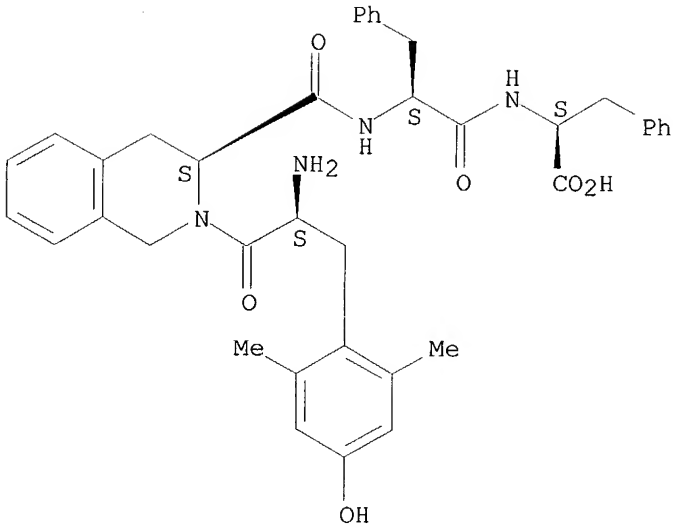
REFERENCE 5: 122:188168

REFERENCE 6: 122:71781

L16 ANSWER 164 OF 164 REGISTRY COPYRIGHT 2004 ACS on STN
RN **156219-37-3** REGISTRY
CN L-Phenylalanine, 2,6-dimethyl-L-tyrosyl-(3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-L-phenylalanyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Phenylalanine, 2,6-dimethyl-L-tyrosyl-L-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-L-phenylalanyl-
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C39 H42 N4 O6
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Conference; Journal; Patent
RL.P Roles from patents: BIOL (Biological study); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); PROC (Process); PRP (Properties)

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

Absolute stereochemistry.




4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 133:12871

REFERENCE 2: 129:245476

REFERENCE 3: 122:188168

REFERENCE 4: 121:50365

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